UNIVERSITY OF LONDON THESIS

Degree PhD Year 2006 Name of Author TRINKLER IRIS.

Hippocampal-dependent Spatial and Episodic Memory in Humans

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Thesis Submitted to University College London
for the Degree of Doctor of Philosophy in Neuroscience

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Acknowledgements

This thesis was funded by the UCL Graduate School and the ORS Award Scheme. The first year was additionally supported by the Fonds zur Förderung des akademischen Nachwuchses, University of Zurich, Switzerland.

I wish to thank Faraneh Vargha-Khadem and Lisa Cipolotti for allowing us to conduct research with patients under their care, and thank the patients, especially Jon, and other volunteers for taking part in this research. I am very thankful to the Functional Imaging Lab for their support of the fMRI studies we conducted.

Many vivid and personal episodic memories accompany this thesis. The Workshop on Navigation in Biological and Artificial Systems in Tübingen comes to mind, where my collaboration with Neil Burgess' Space and Memory Group was "engineered". I owe Neil Burgess and his colleagues my sincerest thanks. Neil Burgess for his invaluable support, advice and constructive criticism, for his stoicism and humorous transcendence towards my more unconventional ideas, and for his meticulousness and patience revising my work. Tom Hartley, John King, Hugo Spiers, Caswell Barry, Jack Kelly, Daniel Haun, Mikkel Wallentin, Christian Doeller, Simon Lambrey, Chris Bird, John O'Keefe, Colin Lever, Steve Burton, Francesca Cacucci, Dmitry Laptev and Ali Jeewajee for creating such an enjoyable work environment and providing relentless technical, theoretical and practical, professional and motivational support, from whom I learned so much from the day I first arrived to do an undergraduate project with Tom Hartley to the last night as I am printing out this work.

Very special and warmest thanks to Jay Gottfried for expanding my world of olfaction and a very rewarding collaboration. I would also like to thank Mick Rugg as my secondary supervisor of the first years. Further I would like to thank the staff and research members of the ICN for support in areas as manifold as providing explanations for the function of BA10 to providing storage space for personal belongings, help with administration and network connections, and for welcoming me back from my trip abroad with a friendly smile.

Finally I would like to thank my family and friends at home for their primary support, their endurance of my absence, and for their interest and curiosity in my studies of memory here in London.

Abstract

The role of the human hippocampus in spatial and episodic memory was investigated using methods from neuropsychology, experimental psychology and functional magnetic resonance imaging (fMRI). The provision of allocentric representations in spatial memory and context–dependent memory for episodic events were each investigated, both for themselves and with the aim of identifying any commonalities in hippocampal function.

Inspired by the similarity of human memory for location and the allocentric representations in the hippocampi of freely moving rats, a difficulty-matched spatial memory test was developed to compare allocentric performance requiring viewpoint-independent representations of location with performance for which viewpoint-dependent representations suffice. It was shown that hippocampal damage leads to a specific impairment in the allocentric condition. This test also indicated that topographical disorientation can result from a selective deficit in allocentric spatial memory, and is under continued development for early detection of Alzheimer's disease.

Episodic memory was investigated in three ways. First, the way in which different aspects of an event are bound together, holistic or fragmented, was investigated using a virtual reality test of context-dependent memory. We found fragmented representations and distinct retrieval hierarchies. Second, the hippocampal involvement in personally relevant memories was investigated with fMRI, using personally known, famous and unknown faces as cues. Extensive hippocampal activation was found for both personally known and famous faces, most likely reflecting the vividness and semantic embedding of memories cued by these stimuli. Third, hippocampal involvement in multimodal context-dependent memory was investigated using fMRI of memory for events occurring in different spatial and olfactory contexts. Extensive, partially overlapping, hippocampal activation was associated with retrieval of both types of context.

The results are discussed in terms of the hippocampal role in memory, its laterality, and the relationship between viewpoint independence, multi-modal context and semantic embedding in retrieval.

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Chapter 1) General Introduction

This thesis investigates memory that is dependent on the hippocampal formation. This medial temporal lobe structure receives input from uni- and polymodal sensory processing areas, thus represents a "multisensory junction". Moreover, some neurons within the hippocampal formation have long been known to contain synapses that are susceptible to lasting changes, forming traces of information passing through, "building memory".

I used various methods to achieve a better understanding of human hippocampal memory, drawing together findings from neuropsychology, experimental psychology and neuroimaging. I am not the first to attempt advancing our understanding in this field, the hippocampus is possibly one of the most prominent brain structures studied, not least because its impairment has such a devastating effect on everyday memory function. In 1957, a report was published describing severe anterograde amnesia in several patients, one of whom was patient H.M., who had undergone medial temporal lobe resection in the hope that it would relieve his intractable epilepsy (Scoville & Milner, 1957). Following the operation, H.M. only remembered things from the distant past, had lost his recent memories and could hardly encode any new information.

This finding of the dependence of memory for everyday events on the medial temporal lobe in humans was paralleled with the discovery of hippocampal place cells in rats (O'Keefe, 1976; O'Keefe & Nadel, 1978). Place cells are selectively responsive to the spatial location of the animal with respect to the environment, independent of the animal's body-axis and heading (Burton et al., 2000; Eichenbaum et al., 1989; Morris et al., 1982; Muller et al., 1994). Place cells are thus represented in an allocentric as compared to an egocentric framework. On the basis of the characteristics of place cells, O'Keefe and Nadel (1978) suggested that the hippocampus functions as a cognitive map. From there we derive a role also of the *human* hippocampus in spatial memory.

Pursuing the advance of our understanding of the hippocampal role in both everyday event memory and spatial memory, this thesis covers spatial memory in Part I, and episodic memory in Part II, and in the end attempts to synthesise the findings of both branches into an overall theory of human hippocampal function.

Overview of individual thesis chapters

Following the General Introduction, I provide a separate introduction to spatial memory with the Introduction to Part I (Chapter 2). It provides background knowledge for the experimental Chapters 3 to 5, introducing the components of spatial representations and their neural bases, the distinction between egocentric and allocentric representations, the clinical disorder 'topographical disorientation' and neuropsychological paradigms used for testing egocentric and allocentric representations in the assessment of this syndrome. Among these neuropsychological paradigms, the Introduction to Part I reports recent findings on egocentric and allocentric representations in a patient, Jon, with focal hippocampal pathology (Vargha-Khadem et al., 1997). Finally it introduces 'Alzheimer's disease' in which topographical disorientation tends to mark an early symptom. I discuss assessment of Alzheimer's disease and one obstacle in early diagnosis of Alzheimer's disease, namely the normal decline of cognitive abilities with age and brain changes in normal ageing as assessed using structural neuroimaging.

Following the Introduction to Part I (Chapter 2), Chapter 3 introduces the development of a topographical memory paradigm using virtual reality. In it, egocentric and allocentric spatial representations for the location of objects are contrasted. Patient Jon's performance on this test is compared to a group of age- and IQ-matched healthy control subjects. In Chapter 4 this paradigm is used for assessing spatial memory in an elderly patient with topographical disorientation. It is hypothesised that impairment of the hippocampus and related areas are the likely origin of her deficit. Early signs of hippocampal malfunction are moreover symptomatic of the onset of progressive dementias such as Alzheimer's. Chapter 5 illustrates the further development of the topographical memory paradigm as it is adapted for possible use in the assessment of early Alzheimer's. The final chapter of Part I (Chapter 6) discusses the conclusions to be drawn from the spatial memory investigations.

Part II focuses on the hippocampal role in long-term memory for everyday events. Investigations that followed Scoville and Milner's (1957) discovery found that hippocampal damage majorly compromised the recall and encoding of *events* whereas its role in factual knowledge acquisition and retention is less clear. Tulving (1972, 1983) coined the labels 'episodic' and 'semantic' memory to refer to these different types of memory respectively. The Introduction to Part II starts with a discussion of episodic memory structure with regards to the binding of various contextual elements with the content of an event-memory, a topic that is investigated in Chapter 8 by means of a recognition memory paradigm using virtual reality.

Another important distinction that was drawn, within memory for events, is context-dependence in contrast to recognition memory that can be based on a feeling of familiarity (Aggleton & Brown, 1999). The Introduction to Part II (Chapter 7) continues by introducing Aggleton and Brown's theory of the "extended hippocampal system". It then moves on to the neural basis of episodic memory as established by neuroimaging studies, including a short discussion of structures other than the hippocampus that are involved in this type of memory. Within that section, I discuss the observation of absence of hippocampal activation in early neuroimaging experiments on episodic memory, introducing the rationale behind the investigations of Chapter 9 and 10. Namely, it encouraged the investigation of the differences between laboratory-based episodic memories and real-world autobiographical memories – discussed in Chapter 7 with an emphasis on personal relevance, memory age, emotional salience and multimodality. Chapter 9 presents an fMRI study exploring hippocampal involvement in memory retrieval cued by personally relevant stimuli (photographs of friends) as opposed to generally known stimuli (photographs of famous people) or pictures of unknown people, thus addressing the characteristics of *personal relevance*, *memory age* and *emotionality* of autobiographical memories. It further looks at the influence of personal or public knowledge about stimuli upon subsequent recognition memory. By contrast, the characteristic of *multimodality* inspired an fMRI study, described in Chapter 10, looking at hippocampal activation for the retrieval of olfactory and spatial context-information of virtual reality-based event memories.

The Discussion of Part II (Chapter 11) summarises the insights from the three investigations into these aspects of episodic memory. Finally, the General Discussion (Chapter 12) draws together the conclusions from Part I and II regarding the hippocampal role in spatial *and* episodic memory, a bridge that has already been envisaged by the Cognitive Map theory (O'Keefe & Nadel, 1978, Chapter 14) and its successors (Burgess et al., 2002). This thesis tries to add some gap-filling bricks to this bridge in an attempt to integrate the diverse aspects of hippocampal function into a more coherent whole.

This General Introduction now starts with an anatomical overview of the localisation and structure of the hippocampal formation. Next, I introduce the most prominent theories of memory systems, including concepts of the Cognitive Map theory (O'Keefe & Nadel 1978), Tulving's semantic-episodic memory distinction (Tulving, 1972; 1983), Squire and colleague's Declarative Memory Theory (Manns & Squire, 1999; Squire & Zola-Morgan, 1991; Zola et al., 2000), Eichenbaum's relational memory theory (Eichenbaum, 2001; Eichenbaum & Cohen, 2001), Marr's hippocampo-cortical model of memory (Marr, 1971), and finally some recent developments of the Cognitive Map theory (Burgess et al., 2002).

The hippocampus - anatomy

The hippocampal formation is situated in the medial temporal lobe, adjacent to the amygdala, surrounded by perirhinal and parahippocampal cortices, see Fig. 1.1. Caudally, the hippocampus ultimately ends around the splenium of the corpus callosum. It's form, reminiscent of a seahorse (see also Fig. 1.1), gave it its name.

Following the terminology of Amaral and Insausti (1990) the 'hippocampal formation' includes the entorhinal cortex, the dentate gyrus (DG), the Hippocampus proper (cornu ammonis; CA3 – CA1) and the subicular complex. (However, other authors do not include the entorhinal cortex here). The major justification for the grouping adopted here is that the subfields are linked by prominent and largely unidirectional connections that appear to unite them as a functional entity (Amaral & Insausti, 1990), see Fig. 1.2. The hippocampus has two major inputs: Afferents from uni- and largely polymodal sensory processing areas converge on the entorhinal cortex mostly via perirhinal and parahippocampal cortices. *Sub*cortical inputs enter

the hippocampal formation via the fornix. Major output projections from the hippocampus go back via the subiculum and the entorhinal cortex to polymodal association areas. The only subcortical outputs of the hippocampus proper are a bilateral and a unilateral projection to the lateral septum from CA3 and CA1, see also Fig. 1.2. Perirhinal and parahippocampal cortices project densely to the entorhinal cortex, and provide nearly two thirds of the cortical inputs to the entorhinal cortex. The dentate gyrus receives its major input from cells located primarily in layers II and III of the entorhinal cortex that give rise to the perforant path. Neurons of this pathway perforate through the subicular complex and hippocampus proper to terminate in the molecular layer of the dentate gyrus.

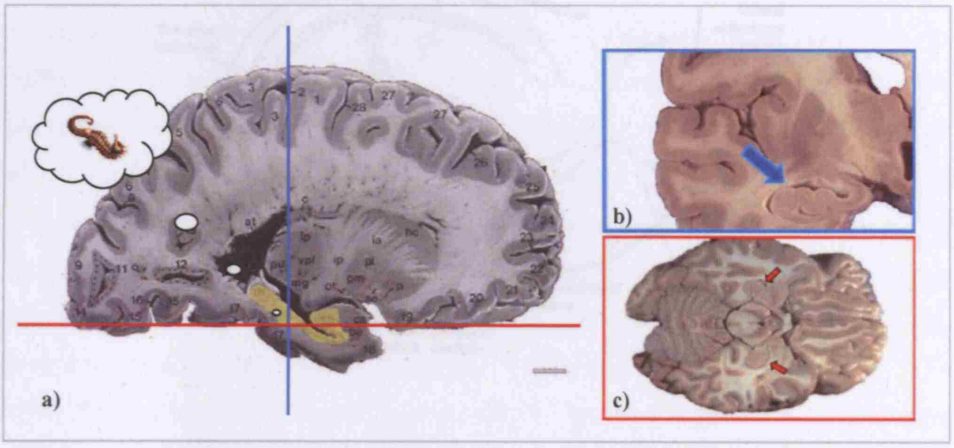


Figure 1.1 Illustrations of the hippocampus: **a)** Saggital view of the brain showing the hippocampus (in yellow), resembling the shape of a seahorse. Tail (th) and head of the hippocampus (hh) are marked. Adjacent structures shown include amygdala nuclei (ba and ca) and the parahippocampus, marked '17' (Illustration modified from Duvernoy, 1999, p. 305). Perspectives of the views b) and c) are indicated by respectively coloured cutting lines. **b)** Coronal view of the hippocampal structure, indicated by the blue arrow. **c)** Axial view of the left and right hippocampus, indicated by the red arrows.

Thereby they form synapses on the distal apical dendrites of the pyramidal cells of the subiculum, CA1 and CA2/3 in passing (Amaral & Insausti, 1990). Cells of the dentate gyrus do not project outside of the hippocampal formation. They terminate, via the mossy fibres, on cells of the dentate gyrus' own polymorphic layer and onto the proximal dendrites of the pyramidal cells of the CA3 region. Collaterals of single CA3 pyramidal cells project to other levels of CA3, to CA1 and to subcortical

regions, especially the septal nuclei. The CA3 field additionally contains several types of nonpyramidal (inter-) neurons with varying connectivity. The border between CA3 and CA2 is not readily apparent (in Nissl-stained sections) because CA3 cells appear to extend under the border of CA2 for a short distance. The CA2 region has the most compact and narrow pyramidal cell layer of the hippocampus, and has no mossy fibre input. CA1 pyramidal cells, to which the Schaffer collaterals project from CA3 and CA2, do not project significantly to other levels of CA1. They project predominantly to the subiculum. The subiculum, in turn, projects to the pre- and parasubiculum and all three project back to the entorhinal cortex.

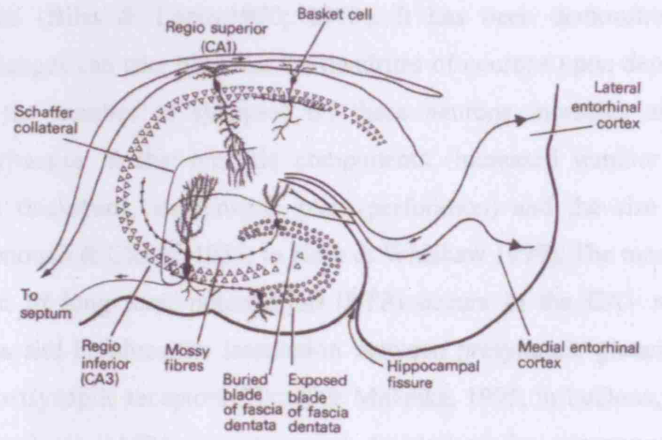


Figure 1.2 Schematic diagram illustrating the different subregions and connections of the hippocampal formation (from O'Keefe & Nadel 1978, p.108).

The subiculum further reaches the medial prefrontal cortex, septum, nucleus accumbens, anterior thalamus, mammilary nucleus, amygdala and stria terminalis. Projections that comprise the basic "trisynaptic circuit" (see Fig. 1.2) from the entorhinal cortex → dentate gyrus → CA3/2 → CA1, have relatively limited spread along the rostro-caudal axis of the hippocampus, i.e., if ~500µm slices were to be cut perpendicularly, the fundamental circuit would remain intact in each slice. This has become known as the "lamellar organisation" of the hippocampus and dentate gyrus. Recent studies however have demonstrated that distant levels of the dentate gyrus and hippocampus are linked by associational connections, too. The modern notion is that only the mossy fibre projection from the granule cells to the CA3 pyramidal cells maintain a lamellar trajectory and distribution (Amaral & Insausti, 1990).

Apart from the mossy fibers from the dentate gyrus granule cells to the hippocampal pyramidal cells, the hippocampal projections consist of thousands of convergences and divergences containing 'Hebb-modifiable synapses' (Kolb & Whishaw, 1999). Hebb proposed "when an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased" (Hebb, 1949; Kolb & Whishaw, 1999). Later, a potential model for Hebbian plasticity was discovered in the perforant path synapses onto the dentate gyrus (Bliss & Lomo,1970; 1973). It has been demonstrated that the following changes can take place on the dendrites of neurons upon depolarisation at a synapse: the number of synapses on these neurons increases and there are qualitative changes in the synaptic components (increased number of vesicles, postsynaptic thickening, subsynaptic plate perforation) and the size of dendritic spines (Greenough & Chang, 1985, in Kolb & Whishaw 1999). The most extensively studied form of long term potentiation (LTP) occurs in the CA1 region of the hippocampus and involves the interaction between presynaptic glutamate and two classes of postsynaptic receptors (Nicoll & Malenka, 1995, in LeDoux, 2000). First, glutamate binds to AMPA receptors and depolarises the postsynaptic cell. The depolarisation allows glutamate to bind to the N-methyl-D-aspartate (NMDA) class of receptors. Calcium then flows into the cell through the NMDA channel and triggers a host of intracellular events that ultimately result in gene induction and synthesis of new proteins (Dudai, 1989; Huang et al., 1996; Kandel, 1997; Nicoll & Malenka, 1995, in LeDoux, 2000). These then help stabilise the changes over a long periods of time. LTP forms the dominant synaptic model of memory.

In the next section, I discuss the cognitive theories of hippocampal memory systems most relevant to this thesis.

Theories of memory systems

Based on the finding that cells in the rat hippocampus respond selectively to the animal's current location irrespective of heading, O'Keefe and Nadel (1978) formulated the Cognitive Map theory in which they propose two memory systems. One, the locale system, is hippocampal-dependent, and the other, the taxon system,

hippocampal-independent. In the locale system, information is entered into a mapping system on an all or nothing basis. There is no increment of the strength of a (spatial) memory on subsequent exposure. There is also little interference when similar (spatial memory) items occur in different parts of an environment. An important characteristic of the locale system is that it provides multiple channels of access for the retrieval of any of the relationships embodied in the map, such that any relationship in the map can be retrieved by activating any other portion of the map, whether or not these relationships were noticed at the time of input (see O'Keefe & Nadel, 1978, p.384). We will return to this notion in the discussion of binding in context-dependent episodic memory which forms the content of Chapter 8.

By contrast, in the taxon system strategies for remembering spatial information are route strategies like the guidance hypothesis "walk around that ladder over there" or orientation hypotheses "look 15 degrees to the left", in which attention is directed to a particular landmark or object (e.g. the ladder) and the navigating individual is required to maintain a certain egocentric relationship to it. The major implications of the taxon system are that information is stored on the basis of category inclusion such that terms with similar features are stored in same or neighbouring neural circuits, incrementally. For this reason, taxon-based memories are prone to interference between similar items and the strength of the memory trace depends on the time elapsed since it has been activated. Each activation of information is thought to result in a small change in synaptic strength.

In the extension of the Cognitive Map theory to humans, O'Keefe and Nadel oppose "memory for items independent of time or place of their occurrence" in the taxon system with "memory for items within a *spatio-temporal context*" in the hippocampal locale system (1978, p.381, footnote). The authors thereby directly refer to Tulving's semantic-episodic memory distinction. Tulving (1972) stated that "episodic memory receives and stores information about temporally dated episodes or events and temporal-spatial relations among these events" (p.385), and that this kind of context-dependent memory is anatomically and behaviourally dissociable from context-free semantic memory. Tulving's theory further proposed a directionality of dependence of the two systems of the kind that new episodic learning is dependent upon semantic knowledge of the items or concepts to be

remembered (Tulving, 1983; 1995). According to O'Keefe and Nadel (1978), the allocentric spatial representations of the hippocampus in rats are hypothesised to have become the framework for the episodic memory system in humans by providing spatial context and making use of the additional inputs of a linear sense of time and language. Further, a lateralisation of these two additional inputs is proposed, namely of temporal input on the right and verbal/ linguistic input on the left. We will return to this lateralisation hypothesis below.

Regarding Tulving's idea that context-dependent episodic memory and context-free semantic memory rely on different neural systems, there is some clinical evidence suggesting that the two don't rely on the hippocampus to the same extend. Typically, amnesic patients with *medial* temporal lobe pathology can present with selective impairment of experiential memory in the context of preserved facts knowledge. By contrast, a smaller number of patients show poor retrieval of semantic knowledge despite recall of autobiographical events (see Graham et al., 2003, for an overview of the literature). For this condition the term semantic dementia has been coined (Snowden et al., 1994). It is often correlated with atrophy in the (left) *lateral* temporal lobe, whereas the medial temporal lobe is spared, at least at initial stages of the illness. It seems however, that a clear differentiability applies only for the extreme forms of context-rich episodic (autobiographical) memory on the one hand and highly abstract factual knowledge on the other. There are less clear forms of memory, like general events memory or autobiographical facts memory, etc., which raise the question whether the episodic-semantic distinction could also refer to two ends of one spectrum.

Investigations with semantic dementia patients (see e.g. Graham et al., 2003 for a recent review; further see Westmacott & Moscovitch, 2003) provide further insight into a possible involvement of the different temporal lobe structures in these forms of memory. Apart from preserved memories about events, semantic memory patients also show intact knowledge of "autobiographical objects" like e.g. of their own teapot that they use daily, albeit they may fail to retrieve the name or function of a similar object of the same category (Snowden et al., 1999). For example, patient K.E., reported by Snowden et al. (1999) uses household objects entirely appropriately in her daily life, yet does not understand their verbal labels, fails to

recognise alternative examples of the same object and shows impoverished recognition of her own objects when they are presented out of context. Thus, experience with an object does not have a general effect of refreshing pre-existing semantic representations of the object category; knowledge is constrained by the experience itself. Snowden et al. (1999) argue that the key factor determining the availability of previously established knowledge is not the time of acquisition but its relevance to contemporary autobiographical experience. Episodic experience serves to reinstate, update or modify existing concepts. Thus, complementary to Tulving's original idea (1983; 1995), there is evidence that semantic memory seems to build on episodic information. And one important mechanism hypothesised to be impaired in semantic dementia is the automatic generalisation of the exemplar occurrence of an object from a particular autobiographical context.

Complementarily, it has been reported that among others, a patient with developmental amnesia, Jon (Vargha-Khadem et al., 1997), despite not remembering information about autobiographical events, showed relatively spared acquisition of facts memory as testified by his GCSE in history. The debate is however ongoing, whether spared acquisition was supported by some remaining hippocampal functionality or indeed provides evidence for the argument that it does not rely on the hippocampus. Such controversy is the ground on which an alternative memory theory prospers that does not distinguish between episodic and semantic memory in respect of the role of the hippocampus:

The Declarative Memory Theory (Manns & Squire, 1999; Squire & Zola-Morgan, 1991; Zola et al., 2000) views the medial temporal lobe as supporting all forms of explicit memory, including episodic and semantic memory, in an undifferentiated manner. The theory builds directly on early findings from patient H.M. and subsequent medial temporal lobe memory models from monkey lesion experiments. The first major claim is that a range of non-declarative memory processes are subserved by regions outside the medial temporal lobe (Squire & Zola-Morgan, 1991). (The way long-term memory is divided into declarative (explicit) versus non-declarative (implicit) memory is illustrated in Fig.1.3.) About this part of the Declarative Memory Theory there is general agreement (but note recent neuroimaging evidence - e.g. Degonda et al., 2005; Gottfried & Dolan, 2003; Henke

et al., 1999 - for a possible human hippocampal function in supporting relatively automatic retrieval of semantic associations), as well as about the proposal of the theory that the amygdala does not contribute to explicit memory (Squire & Zola, 1991).

Another claim concerns the role of the hippocampus in declarative memory. Based on animal lesion experiments using the delayed nonmatching to sample task as the major paradigm for the study of episodic memory, it is stated that monkeys with lesions of the hippocampal formation are equally impaired on that task as monkeys with lesions including the neocortex adjacent to the hippocampal formation, i.e. the perirhinal and parahippocampal gyrus (summarised in Squire & Zola-Morgan, 1991). Thus, the theory does not attribute a more specific role in declarative memory to the hippocampus within the medial temporal lobe memory system. (Note that it is very difficult to lesion the hippocampus selectively and that adjacent cortices often experience some damage.) The authors emphasise that the whole hippocampal region (hippocampal formation plus surrounding areas) is essential for establishing

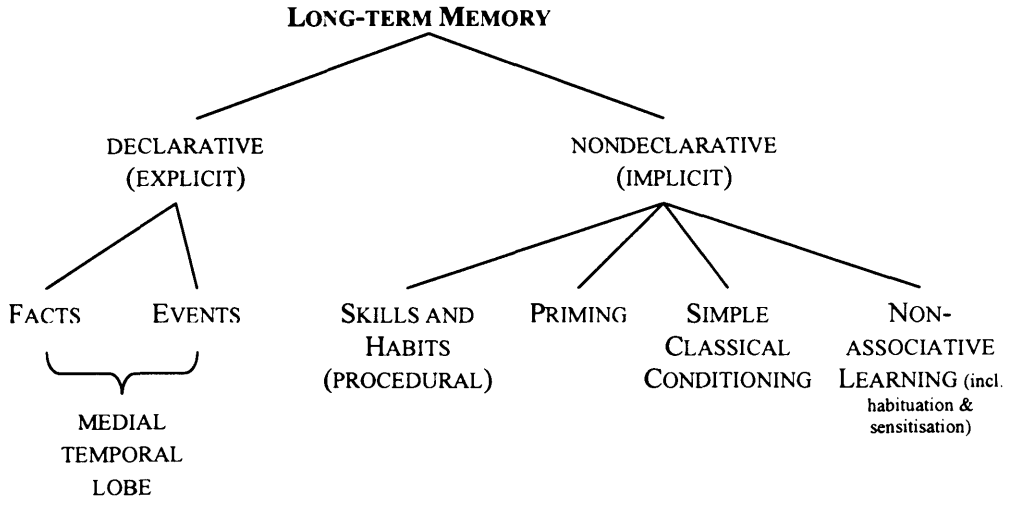


Figure 1.3 Squire & Zola-Morgan's Memory Tree (Squire & Zola, 1996): Declarative (explicit) memory refers to conscious recollections of facts and events and depends on the integrity of the medial temporal lobe. Nondeclarative (implicit) memory refers to a collection of abilities in which experience alters behaviour nonconsciously without providing access to any memory content. This is thought to be independent of the medial temporal lobe.

long-term memory for facts *and* events by virtue of widespread reciprocal connections. Evidence for the Declarative Memory Theory in humans is reported from Gabrieli et al. (1988): Patient H.M. shows impaired learning of definitions of words that had entered general vocabulary, thus semantic memory (however, H.M. has huge lesions) – this similar pattern is shown by Squire and colleagues as observed in selective hippocampal patient G.D. (Shimamura & Squire, 1987) but also elsewhere (patient V.C., Cipolotti et al., 2001).

These findings contrast with those reported above about selective semantic impairment with intact memory for episodic information and vice versa. Not least on the basis of observations as reported in patient Jon (Vargha-Khadem et al., 1997) but also others (Glisky et al., 1986; Hayman et al., 1993; Kovner et al., 1983; Shimamura & Squire, 1987; Tulving et al., 1991), Tulving (2001) proposed that new information may enter semantic memory through the perceptual system independently of medial temporal lobe/ diencephalic brain structures damaged in amnesia. In return, Squire and Zola (1998) claim that actual strong evidence for this theory is lacking. Specifically in the cases presented by Vargha-Khadem et al. (1997) damage to the hippocampus is limited and some patients show residuals of episodic memory acquisition. Squire and Zola (1998) admit however that there seems to be a weak dissociation, between much more severely impaired episodic memory and relatively spared semantic memory. Again, the information about lesion sites is not ultimately conclusive. While Squire and Zola (1998) do not give up the declarative theory, they concede that the "proposal that episodic and semantic memory are affected differently in amnesia [...] is an interesting idea", yet waits for conclusive evidence (Squire & Zola, 1998, p.210). I would like to add to this as a final remark that the kind of semantic memory assessment used by Squire and colleagues needs to be scrutinised. For example, a study by Hamann & Squire (1995) employed a three word sentence completion test that very closely resembles old conventional word-learning tests as employed to assess episodic memory. It seems as if the concept of semantic memory in their theory may need clarification.

We leave the discussion of the Declarative Memory Theory here and turn to yet another influential theory of the role of the hippocampus in long-term memory that directly criticises the spatial framework of O'Keefe and Nadel's Cognitive Map

theory, instead launching the "flexible-relational" or "memory space" theory (Eichenbaum, 2001; Eichenbaum & Cohen, 2001). It is suggested that the role of the hippocampus is to encode relations among items in memory and to support the organisation of memories within a structured knowledge network. A key and fundamental property of such memory networks is the capacity to make inferences about items that have never been experienced together directly, but are indirectly related within the network structure (Cohen & Eichenbaum, 1993). By thus making generalisations, identifying common features between episodes, the hippocampus mediates the recording of sequential and context-specific information in an effort to solve novel problems. Eichenbaum used an inferential paradigm in rats, the "transitive inference task" (Bunsey & Eichenbaum, 1996; Dusek & Eichenbaum, 1997) to support his theory. In this task, distinctive odorous spices are added to the sand through which rats have to dig to obtain buried cereal rewards. First, animals are presented with pair-wise odour discrimination problems (odour A vs B, odour B vs C, odour C vs D, etc.) and rewarded for selecting the appropriate item in an odour pair (i.e. odour A over B, B over C, etc.). The transitive inference trial subsequently probes a new relation alongside the directly learned relations (e.g. B over D). It was found that intact rats can perform the transitive inference task whereas hippocampal-lesioned animals can only perform the directly learned relations (but see Van Elzakker et al., 2003, for an alternative interpretation, and Li et al., 1999, for a relational task that is hippocampal-independent).

Eichenbaum (2001) claims that his model should apply to other forms of learning, e.g. the Morris watermaze task (Morris et al., 1982). In this task, rats learn to escape from submersion in a pool filled with cloudy water by swimming towards a hidden platform. Training involves trial episodes with different starting points. According to the Cognitive Map theory this enforces an allocentric representation. Eichenbaum instead compares this training procedure to training with overlapping odour-pairs (e.g. A vs B, B vs C) in the transitive inference task. In both paradigms the trials share considerable overlapping information, whereas the use of individual cues remains unique to each particular trial. Thus, in the Morris water maze task, trials from different starting points are seen to share considerable common information, including some of the same spatial cues, whereas the use of individual spatial cues is unique to each type of trial (in an egocentric view), e.g. the rat must swim to the left

of a particular distal cue on some trials which corresponds to the right on swims from the opposite starting point. Instead of embracing the principle of allocentric spatial memory, Eichenbaum stresses codings that reflect common features among distinct episodes (Eichenbaum et al., 1999). In summary, Eichenbaum claims that an attractive characteristic of the flexible relational model is that it offers a set of dimensions that can mediate both the properties of spatial memory (as contained in the Cognitive Map theory) and of other types of memory organisation (in rats and humans, compared to the Cognitive Map theory that foresaw an extension beyond space in humans alone). The Memory Space Model also suggests that the relevant dimensions of space begin as the sequence of place representations experienced as one takes different paths through an environment. Links between path-specific representations would be expected to form when the paths cross. This clearly contrasts with the view of cognitive maps stored in Cartesian coordinates (O'Keefe & Nadel 1978). Eichenbaum's view has the merit that it tries to capture the phenomenon of allocentric space. It remains to be seen how it could contribute to extending the Cognitive Map theory to humans and capturing the characteristics of episodic memory.

Before I discuss some recent developments in understanding human hippocampal memory function arising from computational considerations and observations of functional lateralisation, derived from the Cognitive Map theory, I briefly introduce Marr's hippocampal-cortical model of memory (Marr, 1971), that has proved of great influence to the field.

With regard to the nature of the episodic information stored by the medial temporal lobes, Marr's (1971) model saw the hippocampus as providing a mechanism for the rapid storage of a simple representation of an event via connections with modifiable synapses, from which semantic information could later be abstracted and stored in the neocortex. There, information is thought to be recognised and classified as relevant to the animal (Burgess et al., 2001a; Marr, 1971). Importantly, these simple representations were thought to be formed of only those elements through which an event is later addressed. The generic hippocampo-neocortical model of long-term memory consists of relatively dense recurrent connections and sparse representations in the hippocampus, to enable efficient storage and retrieval (via pattern completion).

Connections between neocortex and hippocampus allow the hippocampal representation of an event to be associated with its sensory details, including reactivation of the representations in different neocortical areas dealing with different sensory modalities. Abstracted semantic representations may also be learned over time in neocortex (Marr, 1970). The recurrent connections within each neocortical area would be sufficient to allow unimodal recognition.

Other authors have suggested that the hippocampus provides a means of binding together elements from multiple sensory streams, stored in different brain regions (e.g. Alvarez & Squire, 1994; Cohen et al., 1997; Damasio, 1989a; Mayes et al., 2001; Mishkin et al., 1997; Moll & Miikkulainen, 1997; Norman & O'Reilly, 2003) and that this is necessary for episodic memory. Indeed, associative memory has been found to be specifically impaired in hippocampal patients when requiring access to cross-modal information (Mayes et al., 2001; Vargha-Khadem et al., 1997) and appears to give rise to hippocampal activation in fMRI (Gottfried et al., 2004). On the other hand, it has been observed that allocentric spatial memory, based on solely unimodal (visual) input is impaired in hippocampal patients, a fact that such theories fail to account for. This leads us back to the Cognitive Map theory and its recent development.

Burgess and colleagues (2002) agree that the necessity of supporting spatial behaviour, such as returning to a goal from a new direction, may have forced the hippocampus to specialise in allocentric memory (O'Keefe & Nadel 1978), which is appropriate to long-term memory in general in being robust to changes in one's position between encoding and retrieval (Becker & Burgess, 2001; Burgess et al., 1999; Milner et al., 1999). However, they have modified the notion of lateralised hippocampal function in humans. The Cognitive Map theory suggested that human episodic memory was supported by the incorporation of a linear sense of time (in the right hemisphere) and verbal/ linguistic inputs (in the left hemisphere) into an allocentric spatial framework. There is much evidence that the *left* hippocampus in humans is involved in the storage of verbal material, for example, memory for paired associates, free recall of word lists, and narratives (e.g. Frisk & Milner, 1990; Milner, 1971; Seidenberg et al., 1993). As O'Keefe (1996) argued, the roots of this verbal role may also have a spatial derivative, i.e., the mechanism of abstracting an

allocentric representation from the egocentric detail of sensory perception may have formed the structural skeleton for storing the gist of the narrative. Further, neuropsychological evidence has shown that *right* medial temporal lobectomy impairs visuo-spatial memory (Abrahams et al., 1997; Bohbot et al., 1998; Pigott & Milner, 1993; Smith & Milner, 1981) and topographical memory (De Renzi, 1982; Paterson & Zangwill, 1945). However, on the basis of the following evidence, the idea of a dissociation between spatial (on the right) and verbal (on the left) aspects of hippocampal memory function is modified by Burgess and colleagues (Burgess et al., 2001b; Spiers et al., 2001b): In a virtual reality experiment of the kind that will be introduced in detail in the Introduction to Part II (Chapter 7), a group of left temporal lobectomy patients showed significantly worse performance than controls on context-dependent memory questions, with no indication of verbal mediation, while right temporal lobectomy patients showed an intermediate level of performance (Spiers et al., 2001b). By contrast, in an experiment tapping spatial navigation abilities, the right temporal lobectomy patients performed worse, in line with evidence from neuroimaging for right hippocampal involvement in navigation accuracy in a virtual reality setting (Maguire et al., 1998a). The interaction between group (left versus right temporal lobectomy patients) and task (topographical versus episodic) was significant with the difference between left and right temporal lobe patients in overall topographical and episodic scores both approaching significance (Burgess et al., 2002, see Fig. 1.4). Burgess et al. (2002) conclude that the dissociation strongly suggests that the *right* temporal lobes are more involved in *spatial* memory and navigation and that the *left* temporal lobes are more involved in context-dependent *episodic* memory.

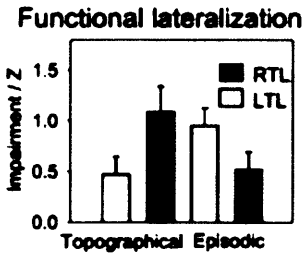


Figure 1.4 Dissociation in performance between right temporal lobe patients (RTL) and left temporal lobe patients (LTL) in topographical and episodic memory. Study by Spiers et al. (2001a), discussed by Burgess et al. (2002).

Building on this basis of previous findings and theorisation, this thesis investigates hippocampal *spatial* memory functions in humans, which we might ascribe to the right hippocampus, in Part I, and hippocampal *episodic* memory functions, hypothesised to be localised on the left, in Part II.

Chapter 2) Introduction to Part I Memory for Space - Hippocampal involvement in allocentric topographical memory

The first part of this thesis concerns the role of the hippocampus in spatial or 'topographical' memory. In this introduction I will first discuss allocentric versus egocentric spatial representations and their components. Following that, I introduce the clinical concept of topographical disorientation whereupon I discuss the neural correlates of different spatial representations, the relationship between them and the role of the hippocampus therein. The attempt has been made to categorise different clinical symptoms that have been classified as 'topographical disorientation' (Aguirre & D'Esposito, 1999). However, that taxonomy does not include selective allocentric spatial impairments. On the other hand, recent investigations in a developmental amnesic with focal hippocampal pathology, Jon, demonstrated such a selective allocentric spatial impairment which was related to impaired hippocampal functioning (King et al., 2002). The paradigm used by King et al. (2002) forms the foundation of the experiments in Chapters 3 to 5 and is briefly introduced here. Chapter 3 presents the development of an improved version of that paradigm which is subsequently used, in Chapter 4, for testing a patient with topographical disorientation who was diagnosed with probable early Alzheimer's disease. Towards the end of this chapter the clinical syndrome of Alzheimer's disease is introduced, in which topographical disorientation is a typical symptom first noticed. Assessing early Alzheimer's is complicated by the fact that, as will be discussed, various cognitive abilities also decline in normal ageing. The experiments conducted in part I lead towards the development of a test to descry people at risk for developing Alzheimer's in the face of this complication, on the basis of contrasting a hippocampal-sensitive and a non-hippocampal-dependent condition in a spatial memory task, presented in Chapter 5. This chapter closes with an overview of other recent investigations into screening elderly people at risk for developing Alzheimer's.

Chapter 2

Egocentric versus allocentric (stored) spatial representations and their components

The differentiation between egocentric and allocentric spatial representations partly maps onto the one between the locale and taxon system in the Cognitive Map theory (O'Keefe & Nadel, 1978). As mentioned in the General Introduction (Chapter 1), the Cognitive Map theory proposed hippocampal involvement in (stored) spatial representations that are independent of (parts of) one's body (retina, head, trunk, etc.), thus allocentric, as opposed to egocentric (O'Keefe & Nadel, 1978). Allocentric spatial memory, in other words, refers to memory for locations defined relative to the environment. This distinction appears under various labels, e.g. 'route based versus more map-like' as defined by Aguirre and D'Esposito (1999) or 'route versus configural' by Siegel and White (1975).

A component of both egocentric or allocentric spatial representations is the perceptual ability that allows recognition of specific locations where navigational decisions are executed, termed 'landmark recognition'. 'Route knowledge' describes the information that encodes a sequential record of movements that lead from the starting point, possibly through decision points, to a destination. Landmarks can be coupled to instructions (e.g. turn left at the gas station), and the learning of landmark-instruction paths is comparable to the learning of chains of stimulus-response pairs. It is anchored in an egocentric co-ordinate frame, if the landmarks are stored in a viewer-dependent way and no information is stored about relationships between landmarks. Such route knowledge is inflexible. Because a route encodes only a series of linear instructions the representation is vulnerable to changes in crucial landmarks. Also, inaccuracies in movement representations might sum up to huge errors. By contrast, allocentric, map-like representations, encoding Euclidian spatial relations between object locations and between locations of objects and the observer, are more robust. They can be generated by combining egocentric spatial decisions with an integrated measure of one's motion in the environment.

Piaget and colleagues proposed that children develop different cognitive representations of space as they age, progressing from initial landmark recognition to egocentric route learning and finally to metric representations of space in the allocentric frame (Piaget et al., 1960). This developmental progression has been confirmed by studies of environmental learning in children (e.g. Acredolo, 1977). Based on the observation of the ontogenetic maturation of topographic representations and from observations of adult performance, Siegel and White (1975) proposed that the development of knowledge about each new environment is characterised by qualitative shifts in the spatial representation from landmark recognition to (egocentric) memory for traversed routes to more abstract, (allocentric) map-like representations of object locations. Thus, the representation is thought to depend on the duration of exposure to an environment, further on the manner in which one was first introduced to the environment (for example by exploration or map reading) and finally on the task performed within it.

The notion that spatial representations in adults ever reach the stage of allocentric representations has been challenged, and alternatively it was proposed that humans represent egocentric distances and directions of objects and continuously update these representations as they move, rather than depending on an allocentric, map-like representation (Wang & Simons, 1999). Wang and Simons (1999) use as evidence for this theory that disoriented participants lose representational coherence between objects of an array, and that without disorientation, an egocentric representation is sufficient. A recent experiment by Burgess et al. (2004) could show however, that such an "egocentric" representation was supported by a consistent relationship between the objects' locations and a landmark available in the testing room. Thus, it is suggested that additional to egocentric representations, representations of locations relative to environmental landmarks are used.

Newcombe et al. (1998) reported that children from an early age (16 months) show the capacity for egocentric spatial updating with help from the room information, but that the integration of landmark information matures slightly later (at 22 months). Nardini et al. (2005) further completed the picture of the development of spatial representations.

They added that egocentric representations that are not updated with movement, such as stored visual images, were present in all children from 3 to 6 years, and spatial updating with help from the room frame of reference was also already used at the age of three and influenced the youngest subjects more than the static egocentric representation. The more difficult task of using a frame of reference intrinsic to the test-array but inconsistent with the external surroundings, a task that also proves hardest to adults (Wang & Simons, 1999), was only solved above chance at 5 and 6 years. It could be argued that whereas spatial updating of egocentric frames of reference refers to route-knowledge, an array-intrinsic frame of reference resembles a map-like representation that is independent of the (updated) viewer's perspective, thus allocentric, and that this capacity matures later in development.

Once established, it is thought that in normal adults egocentric and allocentric representations interlock and work together in order to support spatial orientation and navigation. There are translations from egocentric to allocentric representations at the development of spatial knowledge and back from allocentric to egocentric representations in the direct interaction with the environment. In the case where this interaction is impaired, the assessment of the exact spatial disability affords a careful distinction of the different components.

In the next section I discuss the clinical picture of topographical disorientation which leads me to the neural correlates of spatial representations:

Topographical Disorientation and the neural underpinning of the diverse spatial representations

Over the past century a huge number of case reports have been presented about patients selectively impaired in their ability to find their way within their environment (see Aguirre & D'Esposito, 1999). However, the interpretation of clinical tests used to assess topographical orientation suffers from a lack of a clear differentiation between skills depending on different spatial representations. For example, asking a patient to describe a route in her hometown might rely on different spatial representations for different

routes, as discussed above. As Aguirre and D'Esposito (1999) point out, while subjects may be able to produce a sketch-map of a place, this does not necessarily indicate that they ever possessed an allocentric representation of that place prior to the administration of the test, but rather, a sketchy map could be produced solely on the basis of route knowledge.

In an attempt to distinguish between the various symptoms of topographical disorientation, Aguirre and D'Esposito (1999) offered the following categorisation: a) 'egocentric disorientation', b) 'heading disorientation', c) 'landmark agnosia' and, tentatively, d) 'anterograde disorientation'.

'Egocentric disorientation' is exemplified by a case described by Levine et al. (1985, case 2, cited in Aguirre & D'Esposito, 1999): "When shown two objects, [the patient] made frequent errors in stating which was nearer or farther, above or below, or to the right and left. Spatial imagery was severely impaired." Most egocentrically disoriented patients have either bilateral or unilateral right lesions of the posterior parietal lobe, commonly involving the superior parietal lobule. The differentiation between an impairment of this kind of egocentric spatial representation and other categories of spatial cognition like landmark recognition and 'exocentric' spatial representations, has also been proposed by other authors (Farrell, 1996; Milner & Goodale, 1995), and is originally based on the model of two streams of visual processing (Ungerleider & Haxby, 1994) which states that separable dorsal and ventral areas of posterior cortex subserve the analysis of spatial position ('where') and object identity ('what').

Patients with right parietal damage who present with hemispatial representational neglect (Bisiach & Luzzatti, 1978; Guariglia et al., 1993; see Burgess et al., 2001a) also belong to the egocentric category. They appear to have an intact viewpoint-independent, long-term representation of entire spatial layouts, while their ability to construct a viewpoint-dependent representation in imagery is impaired. From neurophysiological studies in monkeys and rodents there is evidence that cells within parietal cortex maintain representations of object position in one or several (retina, head, trunk, etc.)

egocentric spatial frames. For instance, studies in monkeys found cell firing properties in those areas to represent the position of stimuli in both retinotopic and head-centred co-ordinate space simultaneously (Andersen et al., 1993).

Impairment of 'exocentric' spatial representations and landmark recognition is divided into two categories with their separate underlying neural substrates by Aguirre and D'Esposito (1999); 'heading disorientation' and 'landmark agnosia'. The rarely occurring impairment of 'heading disorientation' results in the inability to derive directional information from landmarks. A patient described by Takahashi et al. (1997), could quickly recognise buildings and landscapes around him and was thus able to determine his current location. However, he was unable to decide *in which direction* he should proceed. On Corsi blocks he performed normally, which contrasts with impaired performance on such tests in the 'egocentric disorientation' group. Patients presenting with 'heading disorientation' are impaired in map drawing tasks and unable to describe routes between familiar locations. The reported lesion site of the patients described in Takahashi et al. (1997) and others (Cammalleri et al., 1996), the right retrosplenial / posterior cingulate region, has been shown to contain head direction cells in the rodent (Chen et al., 1994; Taube et al., 1996), which encode orientation based upon a combination of landmark, vestibular and idiothetic (self-motion) cues. In a recent review of the literature of retrosplenial patients, Maguire (2001b) finds evidence that retrosplenial damage correlated with topographical disorientation is lateralised on the right, in accord with a hypothesised lateralisation of medial temporal lobe function as discussed in the General Introduction (Chapter1) and see also below. Interestingly, in most cases reviewed by Maguire (2001b), the disorientation had resolved by three to eight weeks. Thus, the impaired navigation of patients following damage to the right retrosplenial region was not a permanent deficit and could apparently be overcome (possibly by the collateral side). Maguire (2001b) proposes that the retrosplenial cortex represents the transition zone between egocentric/vestibular inputs from areas such as posterior parietal cortex, and head direction and ultimately allocentric processes in the medial temporal region.

Aguirre and D'Esposito's category of 'landmark agnosia' refers to an impairment of one of those allocentric processes in the medial temporal lobe: While similar to a category proposed by Levine et al. (1985) or Paterson and Zangwill's (1945) 'topographical agnosia', it differs in that it is suggested to be a result of damage to a system specialised for salient environmental features, i.e. landmarks, and not a general object recognition system. Both perceptual and mnemonic substrates are proposed to be damaged in landmark agnosia. According to Aguirre and D'Esposito, this category comprises most cases of 'topographical disorientation' reported in the clinical literature. Such patients present with poor recognition memory for landmarks and spatial scenes and the topographical deficit may well directly result from that. For example, patient A.H. (Pallis, 1955, in De Renzi, 1982), lost his bearings because of his inability to identify buildings and places, though maintaining the capacity to remember the appropriate route between landmarks, as demonstrated by his excellent performance in verbally describing paths and drawing maps. Patient M.S. (Incisa della Rocchetta et al., 1996) performed at chance on three different delayed recognition memory tests that used pictures of complex city scenes, previously unfamiliar buildings and country scenes. He was also found to be impaired at recognising pre-morbidly familiar London landmarks.

More recent neuropsychological studies also associated parahippocampal areas with recognition-based spatial memory, including the recognition of landmarks (Bohbot et al., 1998; Habib and Sirigu, 1987). Other neuropsychological deficits, like prosopagnosia have been noted to accompany 'landmark agnosia'. For example, patient J.C. (Whiteley & Warrington, 1978), failing on a recognition memory test of unknown buildings, displayed a mild impairment in recognising faces, both in real life and on a memory test. Patient A.H. was reported to show considerable agnosia for faces as well as for recognition of animal drawings (Pallis, 1955). However, this connection is not always found and it is likely that the lesion site that produces landmark agnosia is close to but distinct from the lesion sites responsible for prosopagnosia (Aguirre & D'Esposito, 1999). Namely, the lesion sites reported to produce landmark agnosia comprise the medial aspect of the occipital lobe bilaterally or on the right side, involving the fusiform and lingual gyri and sometimes the parahippocampal gyrus. Infarction of

the right posterior cerebral artery is reportedly the most common cause of impairment. Using fMRI, Aguirre et al. (1998) have identified a cortical area that showed a greater magnitude of neural response to buildings compared with other stimuli, including faces. The finding of 'building sensitive' cortex within the anterior, right lingual gyrus has been replicated by others, (e.g. Haxby et al., 1999). Moreover, Epstein and Kanwisher (1998) in an fMRI study, defined the 'parahippocampal place area' (that includes the posterior tip of the parahippocampal gyrus and adjacent regions of the fusiform gyrus, bilaterally). It was shown to respond selectively and automatically to passively viewing spatial scenes such as rooms (even bare walls) and outdoor scenes, but only weakly to single objects and not at all to faces. It is this area that has numerously been implicated in neuroimaging studies in humans that attempted to isolate 'topographical' cognitive processes (e.g. Aguirre et al., 1996; Johnsrude et al., 1999; Maguire et al., 1996b; Maguire et al., 1998b).

The fourth category of 'anterograde disorientation', tentatively suggested by Aguirre and D'Esposito (1999), based on the reports of cases with topographical impairment primarily confined to novel environments, is also thought to be accompanied by lesion sites in the parahippocampus, or at least within the right inferior ventral cortex (Habib & Sirigu, 1987; Pai, 1997; Ross, 1980; in Aguirre & D'Esposito 1999)[1]. The neocortical inputs of this area include inferior caudal visual areas, retrosplenial cortex and the superior parietal lobule (Suzuki & Amaral, 1994). It is thus in a position to associate particular landmarks (represented in ventral occipitotemporal regions) with particular spatial relationships (represented in posterior parietal and retrosplenial cortex) (McNaughton et al., 1989). Neurophysiological studies of the parahippocampal area in freely moving monkeys have identified 'spatial view' cells which respond when the monkey looks at a particular part of the environment (Rolls et al., 1997).

[1] A recent paper has associated this fourth category with processing in the hippocampus and consolidation in connected regions (Turriziani et al., 2003).

Aguirre and D'Esposito's taxonomy (1999) seems to capture the various differences in clinically observed topographical disorientation. Interestingly, there is no category referring to spatial memory deficits caused by hippocampal damage in humans. There don't appear to be numerous clinical cases reporting selective topographical memory impairments based on hippocampal lesions (but see Maguire et al., 1996a). By contrast, the Cognitive Map theory proposed hippocampal involvement in allocentric spatial representations (O'Keefe & Nadel, 1978). In animals this has been corroborated by studies employing electrophysiological recordings in awake and behaving animals (e.g. O'Keefe & Dostrovsky, 1971). Further, hippocampus-lesioned rats are impaired in navigating to a hidden platform from a new location in the Morris water maze (Morris et al., 1982). Also in humans, the hippocampus has recently been found to be implicated in allocentric spatial behaviours similar to those described in other animals (e.g. Abrahams et al., 1997; Ghaem et al., 1997; Hartley et al., 2003; Maguire et al., 1998a; Spiers et al., 2001a). Most intriguingly, in 2003 a group published the finding of 'place cells' clustered in the human hippocampus, recorded via in-depth electrodes in epileptic patients (Ekström et al., 2003). I conducted an experiment, designed by Hartley and Burgess (Hartley et al., 2004, see Fig. 2.1), in which we did not directly assess human place cells, but compared human spatial behaviour to patterns of hippocampal place cell firing in rats. Per trial subjects were presented with a spatial location marked by a flag within a rectangular virtual reality environment with distinct distal landmarks, see Fig. 2.1a). After subjects had explored the

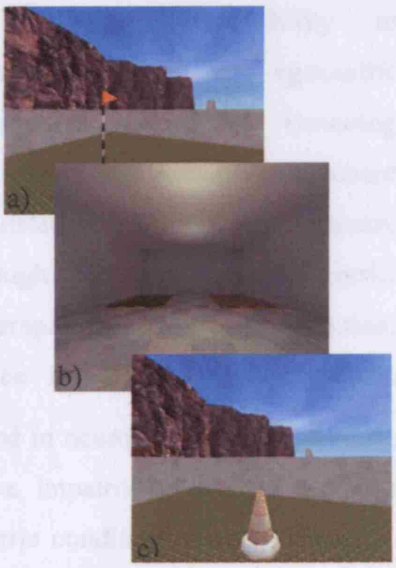


Figure 2.1 Hartley et al. s (2004) virtual reality experiment exploring human spatial learning. Participants learned spatial locations marked by a flag within a rectangular environment surrounded by distinct landmarks (a), were briefly removed from the environment (b), reinstated and had to mark the flag location, while one or both sides of the rectangular environment might have changed in size (c).

environment and learned the location of the flag, they were transported to a different environment (see Fig. 2.1b) and reinstated in the test environment, the shape of which had however changed in some of the conditions. It may have expanded or shrunk on one or both sides. The subjects were asked to place a marker at the location where they thought the flag had been before (see Fig. 2.1c). We could show that the spatial behaviour of our human subjects as a group mirrors place fields in rats, see Fig. 2.2. Moreover, it can be modelled using similar mathematical rules (Burgess & O'Keefe, 1996; Hartley et al. 2000; 2004). We would hypothesise that such behaviour in humans is also dependent on the hippocampus. Particularly, the impossibility to continuously update an egocentric representation, caused by removing subjects from the virtual environment and reinstating them in a new location, is thought to tap an allocentric, hippocampal-dependent representation. Evidence for this has recently been provided in neuropsychological investigations: Feigenbaum & Morris (2004) showed a selective impairment of right temporal lobectomy patients in an allocentric versus egocentric condition of a task using a touch screen with an array reminiscent of the Morris watermaze.

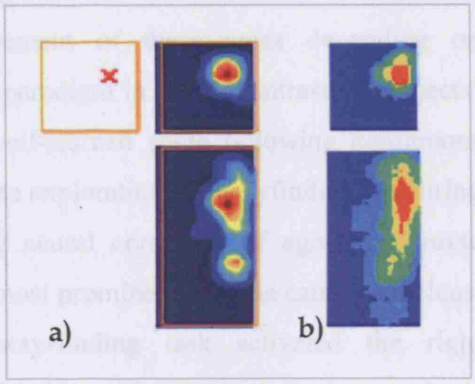


Figure 2.2 Comparison of averaged human allocentric spatial behaviour **(a)**, and 'place fields' derived from 'place cell' firing in the rat's hippocampus **(b)**, in shape-changing environments (Hartley et al. 2004; Burgess & O'Keefe 1996). The smoothed density maps shown in a) summarise the marker locations over all subjects. Here shown is the condition in which the environment changed from a small square to a rectangle.

Further evidence for hippocampal involvement in allocentric but not egocentric spatial representations comes from functional imaging studies. Maguire et al. (1998a) in a PET navigation study, found hippocampal activation specifically during wayfinding compared to following a trail of arrows, thus in allocentric but not egocentric processing of locations in the town. Moreover, right hippocampal activation correlated with the

accuracy of navigation. By contrast, the medial and right inferior parietal areas were found to be globally involved in all movement conditions, in line with a role in translating between allocentric and egocentric representations. Similarly, Iaria et al. (2003), found right hippocampus in navigation using landmarks, and caudate activation when using a non-spatial strategy in a place-learning experiment using fMRI, with the posterior parietal and frontal cortices supporting both conditions. Hartley et al. (2003), extended this finding to differential involvement of these areas depending on wayfinding success: They used a virtual reality paradigm in fMRI, contrasting subjects' neural activity between navigating along a well-learned route (allowing continuous updating of an egocentric representation) and free exploration and wayfinding (requiring an allocentric representation). The underlying neural correlates of egocentric route following in accurate navigators was localised most prominently in the caudate nucleus. By contrast, effective navigators in the way-finding task activated the right hippocampus. Further areas that were found active in wayfinding attempts (uncorrelated with success) comprised parahippocampal and fusiform, retrosplenial and parietal cortices. These correspond to areas involved in landmark recognition, heading orientation and egocentric spatial representations as discussed above. Finally, in a very recent publication, Parslow et al. (2004) also reported hippocampal activation at encoding in an allocentric compared to an egocentric spatial memory condition.

In summary, while animal experiments and recently also functional neuroimaging and neuropsychological investigations in humans have thus corroborated the involvement of the hippocampus in allocentric spatial memory, there is a lack of wider clinical recognition of this involvement. This might be attributed, as mentioned at the beginning of this section, to a lack of sensitive testing of purely allocentric spatial representations (but note other very recent developments, e.g. Feigenbaum & Morris 2004). The experiments that form the content of the chapters 3 to 5 were developed in order to deal with this shortcoming. The underlying paradigm is introduced in the next section and I discuss a previous study that assessed topographical impairment in a patient using this paradigm (King et al., 2002).

Neuropsychological testing of egocentric versus allocentric spatial representations

In an experiment testing memory for object locations, a direct comparison of subjects' egocentric and allocentric spatial representations is possible by contrasting probing memory for object locations from the same viewpoint (allowing either strategy) or from a shifted viewpoint (promoting exclusively allocentric processing if the new viewpoint is introduced abruptly and egocentric spatial updating is prevented). This manipulation is enabled using a virtual reality design (King et al., 2002).

Holdstock and colleagues had attempted before to contrast ego- with allocentric memory in a study of memory for the location of a spot of light in a patient with selective bilateral hippocampal pathology (patient YR, see Holdstock et al. 2000) and in two patients with more extensive bilateral medial temporal lobe damage (Patients RS and NM, see Holdstock et al. 1999). The use of egocentric representations in their study was encouraged by switching off the lights and testing from the same view, while allocentric representations were encouraged by leaving the light on and having subjects move between presentation and recall. A marginally greater impairment for the 'allocentric' condition was found in patient YR. Patients RS and NM were both impaired in the 'allocentric' condition, whereas only RS was also impaired in the 'egocentric' condition. Importantly though, Holdstock et al.'s 'allocentric' task could have been solved using a continuously updating egocentric strategy while moving. It is unclear, whether patient RS's additional impairment of the 'egocentric' task was due to additional cortical (white matter) atrophy.

The virtual reality paradigm developed by King et al. (2002) was used to test Jon, a young and very bright patient who suffered from perinatal anoxia and whose hippocampi are reduced in volume by 50% (Gadian et al., 2000; Vargha-Khadem et al., 1997). He showed selective impairment in the allocentric as compared to the egocentric condition. More exactly, he showed high performance in the same view condition when tested for a short number of object locations at a time (i.e. for short list lengths), with performance decreasing from near ceiling to 50% for list length 10 (chance level was 33%). In the shifted view condition in comparison, he performed at chance for all list

lengths greater than one item. Control subjects performed much better than Jon in the shifted view condition. In the same view condition they showed a ceiling effect. On the one hand we thus notice a selective impairment of Jon in the allocentric versus the egocentric condition. However, as the control subjects' as well as Jon's performance decreased between the same and shifted view task, a selective impairment in some allocentric mechanism could not be conclusively disentangled from a possible difficulty-related impairment. One attempt made by King et al. (2002) to control for this, was to reduce control participants' performance in the same view condition by testing them with a greater number of foil objects. If thus compared, Jon now performed better than control subjects in the same view task and much worse in the shifted view task. However, such a manipulation renders the level of chance performance noncomparable between Jon and the controls. This situation forms the outset of the investigations presented in Chapter 3. The attempt was to match the same and shifted view tasks for difficulty, leaving the chance levels equal for both and without tampering with the conditions' respective ego- and allocentric dependence. As will be reported in Chapter 4, the virtual reality task was further used with a case of topographical disorientation and showed that an allocentric deficit could underlie topographical disorientation in the absence of impaired landmark recognition. The patient tested had suspected early Alzheimer's disease. Upon the findings from Chapter 4, as presented in Chapter 5, our goal was to use our topographical memory paradigm in the assessment of people at risk of developing Alzheimer's disease, the syndrome of which is subsequently introduced. As this is of relevance in view of an association between memory problems and Alzheimer's disease, the last but one section of this chapter discusses memory performance in normal ageing. The last section finally presents other studies that recently attempted to identify early signs in elderly people at risk of developing Alzheimer's disease.

Alzheimer's disease

Among people above the age of 65, the incidence of mild dementia is 3 to 20% and of severe dementia 1 to 6% (Kolb & Whishaw, 1999). More than 65% of people suffering from various types of dementia have Alzheimer's disease.

The pathology is marked by neuropathological correlates such as amyloid plaques consisting of protein material, surrounded by degenerative cellular fragments, neurofibrillary tangles and granulovacular bodies. The cortex becomes atrophied, losing up to a third of its volume. Fox et al. (1996) using digital subtraction of coregistered serially acquired MRI brain scans, taken approximately 1 year apart, determined rates of global and local atrophy in a group of Alzheimer's patients and a healthy control group. The median rate of atrophy was significantly greater in the Alzheimer's group than in the control group. There was no overlap between the groups. Furthermore, three non-demented individuals at risk of familial Alzheimer's disease had scans 6-14 months apart and showed greater rates of volume loss than the controls; these three individuals subsequently developed symptoms of dementia.

According to Kolb and Whishaw (1999) frontal lobes are less affected than posterior cortex, whereas the most extensive changes are seen in the posterior parietal areas, inferior temporal and limbic cortices. More precisely, Braak and Braak (1991) on the basis of extensive neuropathological studies, proposed that the characteristic neurofibrillary tangles of Alzheimer's disease first appear in the transentorhinal region and only later progress to involve the hippocampal formation – entorhinal cortex, subiculum and CA1. The transentorhinal region is a complex transitional zone located between the entorhinal region and the adjoining temporal isocortex. Lesions in this region are critically placed to disrupt connections to and from the hippocampus. On the level of neurons there appears to be a substantial reduction in large cells, which may shrink rather than disappear, manifest in loss of dendritic arborisation. A final attribute of the disease pattern are reductions in different neurotransmitter systems, among which is acetylcholine (Kolb & Whishaw, 1999).

The definition of Alzheimer's disease originates from a case of a 51 year old woman, reported by the German physician Alois Alzheimer in 1906. The present-day diagnosis of *probable Alzheimer's disease,* is based on the criteria of the 'National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease

and Related Disorders Association' (NINCDS-ADRDA, McKhann et al., 1984), defining the dementia syndrome as "deterioration in two or more areas of cognition, including memory, sufficient to interfere with work or social function". The definitive diagnosis of Alzheimer's disease however requires histological examination of brain tissue.

Memory problems are a defining trait and most prominently mark the onset of dementia, in keeping with the anatomical correlate of changes in the transentorhinal region. However, memory, together with other cognitive functions, also fades in healthy aging.

Decline of cognitive abilities in healthy normal ageing

It has been shown in behavioural experiments that autobiographical event memory, decreases with age whereas for semantic memory, the case is less clear (e.g. Nyberg et al., 1996; Piolino et al., 2002). A recent study reported that both episodic and semantic memory changed in higher age, but with semantic memory showing "higher stability coefficients" than episodic memory (Lövdén et al. 2004). Other authors have further excluded decreases in short-term memory, perceptual representation, and procedural memory with age (Nilsson, 2003). In line with the hypothesis that episodic and spatial memory share their neural substrate, namely the hippocampus, allocentric spatial abilities have also been shown to decline with normal ageing, e.g. demonstrated by Driscoll et al. (2005) using a computerised version of the Morris water maze task in a virtual reality environment, but also others (Inagaki et al., 2002; Monacelli et al., 2003). Monacelli et al. (2003) showed that older participants, together with mild Alzheimer's patients, scored significantly lower in spatial orientation compared to young and middle aged participants. Inagaki et al. (2002) reported that elder participants show a performance decrease in mental rotation tasks in which the observer's view has to be rotated around an array as opposed to tasks in which the array itself is rotated.

In consideration of the difficulty to distinguish dementia-related memory decline from age-related decline, several research groups have recently attempted to come up with neuropsychological tests to descry people with early signs of developing Alzheimer's.

This effort is all the more imperative as therapeutic agents for the symptomatic treatment of Alzheimer's disease have been discovered recently, and as therapeutic options to reverse, slow or halt progression of Alzheimer's disease are being investigated (Fowler et al., 2002).

Recent attempts to detect the onset of Alzheimer's disease at an early stage

An overview by Fox et al. (1998) confirms that despite memory decline in normal ageing, memory tests do make the largest contribution to discriminating early Alzheimer's disease from healthy aging. In a careful investigation, the same authors studied a group of 63 individuals at risk of autosomal dominant familial Alzheimer's disease over a six year period to assess the earliest clinical and neuropsychological features of the disease (Fox et al., 1998). Subjects were only included if they and other informants felt they had no symptoms of cognitive decline. During the study, 10 subjects became clinically affected. These subjects were undistinguishable from those who remained well in terms of age, gender, handedness, family history and initial Mini-Mental State Examination. However, they differed in that they scored significantly lower in verbal memory and performance IQ at their first assessment if grouped together in retrospect.

The brain structure of each individual was additionally analysed in blinded assessment, revealing diffuse cerebral and medial temporal lobe atrophy in subjects once they were clinically affected. Fox et al. (1998) concluded that in familial Alzheimer's disease cognitive decline predates symptoms by two to three years before symptoms are manifest and four to five years before individuals fulfil criteria for probable Alzheimer's disease. A further conclusion deems especially *verbal* memory deficits to precede more widespread deterioration, which the authors relate to a possible vulnerability of the left (or dominant) hemisphere in Alzheimer's disease. This would be in line with the reported devastation of delayed recall of verbal material in Alzheimer's disease such that Hodges and Patterson (1995) and Greene et al. (1996) found no significant difference on this measure between patients with very mild and moderate dementia.

However, Fox et al. (1998) used a face recognition test as non-verbal test which may not have afforded hippocampal memory (might instead have afforded extrahippocampal structures).

Another group conducted a very recent meta-analysis to establish effect size over a wide variety of cognitive tests on which preclinical Alzheimer's patients were compared to matched healthy subjects (Bäckman et al. 2005). They claim that episodic memory is not exclusively and sensitively more impaired in individuals with preclinical Alzheimer's disease. Their meta-analysis reveals comparable effect sizes for the domains episodic memory, executive functioning and perceptual speed. To counter this argument, one would have to establish whether the episodic memory tests compared differentiated sufficiently between context-dependent recollection and familiarity-based recognition. I will introduce these concepts in Part II on episodic memory. Here I simply mention that in episodic memory there is an ongoing debate whether there are different aspects of this kind memory, involving the hippocampus to a different degree. This debate is reminiscent of the one that is dealt with in Part I of this thesis, namely about the differential hippocampal dependence of egocentric and allocentric spatial memory. It also plays into the interpretation of two more studies investigating tests sensitive to differentiate between early Alzheimer's patients and healthy aging individuals. Both studies found object–location paired associate learning to be most sensitive for diagnosing early Alzheimer's. Fowler et al. (2002) looked at a group of patients classified as presenting with 'clinically questionable dementia', sometimes also termed 'minimal Alzheimer's disease (Perry et al., 2000) or 'mild cognitive impairment' (Petersen et al., 1999). Such individuals show isolated symptomatic memory problems but unaffected daily functioning. Between 24% to 75% of questionable dementia patients fulfil criteria for probable Alzheimer's disease at later assessment (Fowler et al., 2002). The patients were tested on the CANTAB (Cambridge Neuropsychological Test Automated Battery, Morris et al., 1987). Fowler et al. (2002) found that scores on two subtests of the Visual Memory Battery of the CANTAB, namely the delayed matching to sample and paired associate learning test, classified 88% of early Alzheimer's patients at initial assessment and 100% at 12 month reassessment such that there was no

overlap in scores between deteriorating and stable questionable dementia patients. Swainson et al. (2001) compared performance of a questionable dementia group to a group of healthy control subjects as well as to a group of patients with depression and also found that the questionable dementia patients performed worse than both the depression and control subjects on two recall tests (logical memory and paired associate learning) from the CANTAB, alongside others.

The CANTAB paired associate learning subtest requires subjects to remember patterns associated with different locations on the screen. Six white boxes appear evenly spaced on the screen, and are opened one by one in random order for 3s each. In the beginning only one box contains a pattern. After all boxes have opened, the pattern appears in the middle of the screen and the subject is required to touch the box in which the pattern was located earlier. If correct, the task proceeds to the next set of patterns. If an error is made, the trial is repeated (to a maximum of 10) until the correct choice is made. After two correct sets with a single pattern, the number of patterns is increased to two for two sets, three for two sets, then to six and finally eight for one set each. Whenever subjects make a mistake the whole of that set is repeated.

One difficulty of the test seems to be to decide on a clear measure with which to compare performance. The scales appear somewhat non-linear. For instance, Fowler et al. (2002) used 'total errors to criterion' which denotes how many errors were made before completion of the test and was found to correlate highly with all other measures. However, this required adjusting scores for subjects who did not complete the test, which was 'resolved' adding the error score of the worst subject attempting that set. Further, the apparent sensitivity to early onset of Alzheimer's, associated with impaired hippocampal functioning, is slightly surprising as we hypothesise that this task might be solved using a purely egocentric spatial representation. The discussion of how this task may nonetheless tap an allocentric spatial representation is however postponed to the Discussion of Part I (Chapter 6).

In summary, there is good evidence that (memory) tasks sensitive to hippocampal functioning descry people at risk for developing Alzheimer's disease, regardless of whether these tasks are verbal or spatial. However, it has not been made explicit if it is this hippocampal dependence that makes the tests sensitive and to date there is no easy to use test that directly opposes two conditions of which one is hippocampal sensitive and the other is not. The test developed in Part I tries to fill this gap.

Chapter 3) Development of a topographical memory experiment with difficulty-matched egocentric and allocentric conditions

Introduction

The study presented in this chapter and published in King et al. (2004) builds on a former virtual reality experiment (King et al., 2002) in which it has been shown that a patient with focal hippocampal pathology (Jon, Vargha-Khadem et al., 1997, see also below) showed differential performance on a topographical memory task, depending on whether his memory for object locations was tested from the same view or from a different viewpoint. Patient Jon performed significantly worse than control subjects and not better than chance for lists of more than one item in the shifted view condition. In this condition, the task cannot be solved on the basis of an egocentric representation of object locations, due to spatial updating being disrupted between presentation and test. On the basis of these results it was suggested that the hippocampus is involved in non-egocentric topographical memory (King et al., 2002). However, it could not be ruled out that the difference in performance between the patient and control subjects was due to a non-linear effect of the difference in difficulty between the two conditions, as healthy subjects also showed a decline in performance from the same view to the shifted view condition. A linear effect of difficulty had been ruled out by matching the performance of control subjects in the same view condition to that of the patient by testing them on a higher number of foils. An impairment was still observed in the patient for the shifted view condition when using the different numbers of foils for him and for the controls. The drawback of this manipulation was that it led to different chance levels for the two groups, which made the comparison of performance more complicated. The goal of the study presented in this chapter was to match the two conditions for difficulty in healthy subjects. This included analysis of control data from King et al.'s (2002) study in order to find out how difficulty could be manipulated, especially in the same view condition.

Analysis of King et al.'s (2002) control data

Performance of 12 control subjects was inspected with respect to possible parameters of difficulty. The current analysis looked at trials in which subjects had to choose the correct object location among three foil locations. The focus was on the distance between the foil locations, defined as:

$$d_f = \frac{n}{1/dist1 + 1/dist2 + 1/dist3}$$

As a first qualitative impression, there appears to be a relation between performance and foil distance as averaged over 36 trials of one block on the same view condition. The further apart the foil locations, the higher the performance of that block, see Fig. 3.1. However sensitivity was reduced by subjects performing near ceiling. In a first step I thus varied the numbers of foils in an attempt to bring the performance down from ceiling. The list length was held constant at four items as previous analyses by King et al. (2002) had revealed that normal subjects' performance did not differ between list lengths 4 and 7.

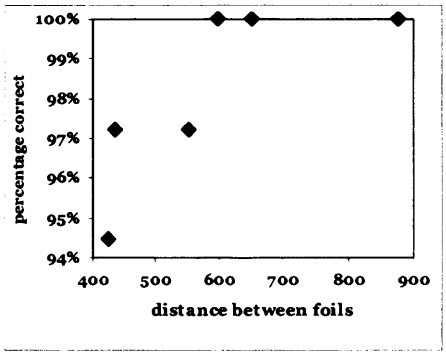


Figure 3.1 Qualitative analysis of the performance in the same view condition of control subjects in the courtyard experiment previously published (King et al., 2002), showing the relation between performance (percentage correct) and average distance between foil locations per block of 36 same view trials averaged over 12 subjects. X-axis displays quake units (for reference, the extent of the environment is approximately 1250 x 1450 units). As can be seen, the further away the foils from the target, the better subjects performed. However, the performance is generally very high.

Pilot Experiment

Participants

20 participants took part in this experiment, 12 females and 8 males, aged 25 on average (stdev. = 6) and scoring 10.1 points out of a possible 12 (stdev. = 1.6) on the Raven's Advanced Progressive Matrices Set I, an approximate test of general non-verbal cognitive processing abilities that has been found to correlate highly with more extensive IQ tests like the Wechsler Adults Intelligence Scale Revised (1986). Informed consent was obtained from all subjects and they were paid £7.50 per hour for their participation.

Procedure

A virtual environment (VE), based on a modified version of the computer game Quake2 (© Id Software, programming: John King, see also King et al. 2002), was used to present subjects with an array of 21 randomly scattered plinths located in a courtyard of a mediaeval array of castle walls, merlons and timbered houses, see Fig. 3.2. The VE was presented on an Intel P3 600MHz computer on a standard 19 inch monitor at a resolution of 800 x 600 pixels and a frame rate of 40 Hz. Before the start of the experimental trials, subjects could explore the sight by wandering virtually along two

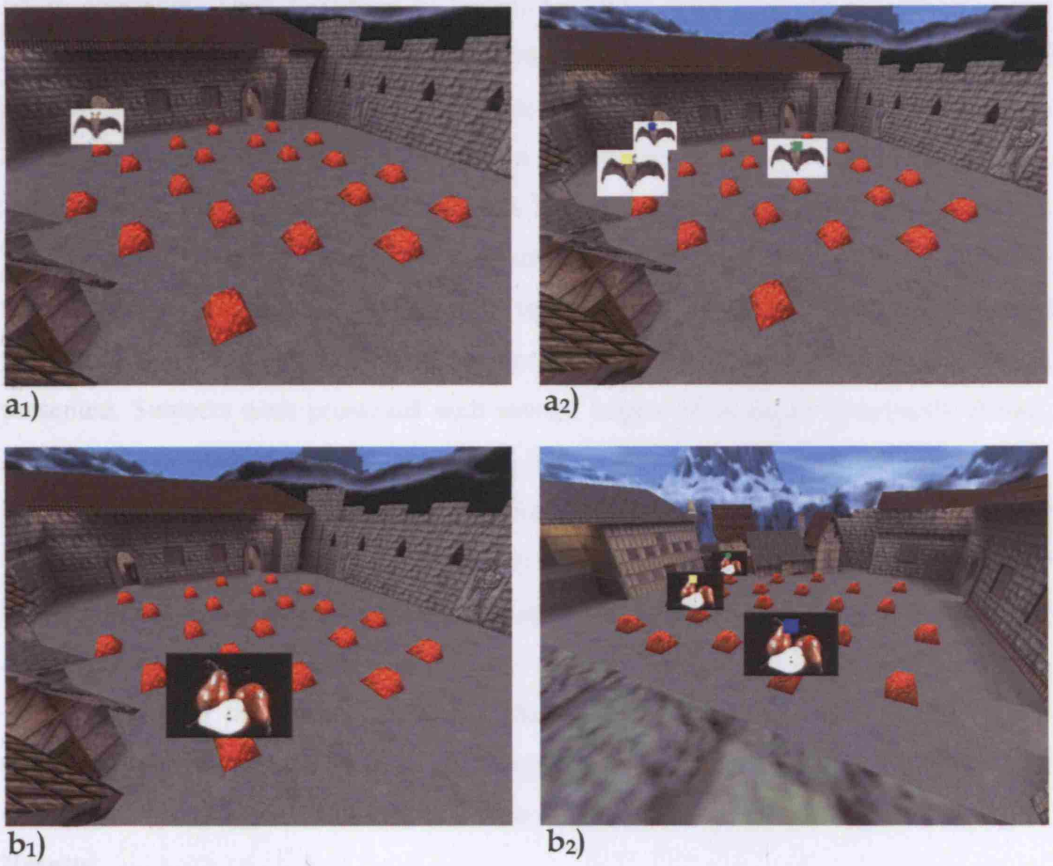


Figure 3.2 Pilot experiment: Snapshots from the courtyard experiment. **a1** Presentation of an object from one view point. **a2** Testing for an item from the same viewpoint with 3 foils. **b1** Presentation of an object from the other viewpoint (presentation happened in each corner of the environment equally often in both conditions). **b2** Testing in the shifted view condition. Note that in this condition a traffic cone across the square on the rooftops marks the viewpoint at presentation.

connected sides of the rooftops of the castle wall arrays. The two viewpoints from which subjects were subsequently tested on the location of objects in the courtyard were placed at each far end of those explorable rooftops. The angle between the two vantage points was chosen to be approximately 140°.

In each trial subjects appeared in the corner between the two explorable sides of the courtyard square and walked to the end of the one side at which a marker was visible. Upon arrival at the marker, the subjects' viewpoint was adjusted to give view to the entire courtyard. Then a number of two-dimensional images of objects appeared one after another for 3s each, with an interstimulus interval of 1s. The actual number of objects presented depended on the *list length* of the trial. Subjects were instructed to name each object aloud as it appeared on the screen and to remember its location. Subsequently, subjects' memory for object locations was probed either from the same view or from the shifted view at the opposite end of the courtyard. In the shifted view trials subjects were instantly transported to the new viewing position. The order of probing objects was random. Testing occurred 5s after the last object had been presented. Subjects were presented with several copies of an object previously shown, located at a number of distractor locations (depending on the *foil number* of the trial). These probe objects were labelled by different colours and subjects had to indicate by choosing the correspondingly coloured key on the keyboard, which copy was at the location in which the object had originally appeared. Subjects responded as quickly and accurately as possible. The presentation for the next series of objects followed immediately after the subjects' response. Same- and shifted view trials occurred in a randomly interleaved fashion. Subjects completed 3 sets each of same- and shifted view conditions at list length 4 with 3, 4, or 5 foils at testing.

Results

The two conditions, same view and shifted view, differed significantly (repeated measures ANOVA, $F_{1,19} = 73.2$, $p<0.001$), there was a significant effect of number of foils ($F_{1,19} = 13.0$, $p<0.01$), and the interaction condition x number of foils was also significant ($F_{1,19} = 5.9$, $p<0.05$). As can be seen from Fig. 3.3, performance dropped with

the higher numbers of foils, however nearly exclusively for the shifted view condition, which increased the difference in performance between the two conditions.

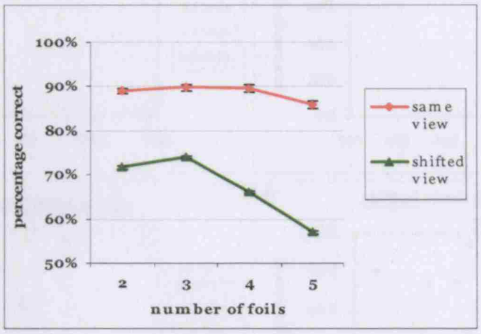


Figure 3.3 Performance results from pilot experiment: Average over 20 subjects as a function of the number of foils, shown separately for same and shifted view conditions. List length =4, error bars show standard error. Performance drops with higher numbers of foils, mainly for the shifted view condition.

As a next step, the data were analysed with regard to the relationship between performance and distance between target and foil objects on the one hand, and the distance between the viewer's vantage point and the target object on the other hand. The distance between target object and viewer was defined per test item and summarised over performance categories (5% intervals). Average foil distance was defined as in the analysis of King et al.'s (2002) data ($d_f = n/(1/d_1+1/d_2+\ldots+1/d_n)$), and was also summarised over performance categories. As can be seen from Fig.3.4a&b, the closer the foils, the worse the performance. Also, in the same view condition it can be seen that the closer the viewer to the target at presentation, the better the performance, see Fig. 3.4c.

Discussion

The main finding of the pilot experiment, in line with analyses of King et al's (2002) control data, was that the difficulty of the courtyard experiment was dependent on the distance between the foil locations at test, and for the same view condition on the distance between the viewer and the target location.

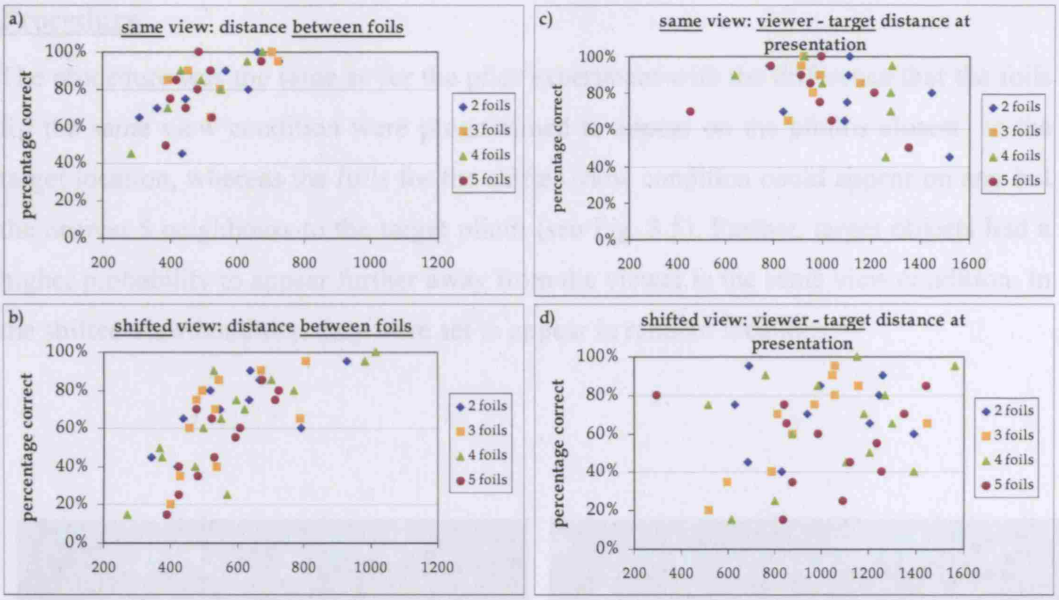


Figure 3.4 Results of pilot experiment: Analysis of relationship between performance and distance between foils (a & b), and distance between viewer and target (c & d), in the same- and shifted view conditions. The average distance is categorised by performance in steps of 5%. In both conditions, the closer the foils to the target, the worse performance (a & b). The closer the viewer to the target at presentation, the better performance. This applies for the same view condition (c), but not for the different view condition in which near at presentation means far at test (d). X-axis displays quake units (for reference: the extent of the environment is approximately 1250 x 1450 units).

Experiment 1: A performance-matched version of the courtyard experiment

On the basis of the results from the pilot experiment the next version of the courtyard experiment was constructed by manipulating the distance between the foils and the distance from the viewer to the object locations, so as to attempt to match performance in the same and shifted view conditions.

Participants:

18 participants, 10 females and 8 males, aged 26 on average (standard deviation = 4.9) and scoring on average 10.9 out of 12 on the Ravens' Advanced Matrices Set I (standard deviation = 1.4) took part in this experiment. Participants gave informed consent and were paid £7.50 per hour for their participation.

Procedure

The procedure was the same as for the pilot experiment with the difference that the foils for the same view condition were programmed to appear on the plinths closest to the target location, whereas the foils for the shifted view condition could appear on any but the nearest 5 neighbours to the target plinth (see Fig. 3.5). Further, target objects had a higher probability to appear further away from the viewer in the same view condition. In the shifted view condition they were set to appear in random locations.

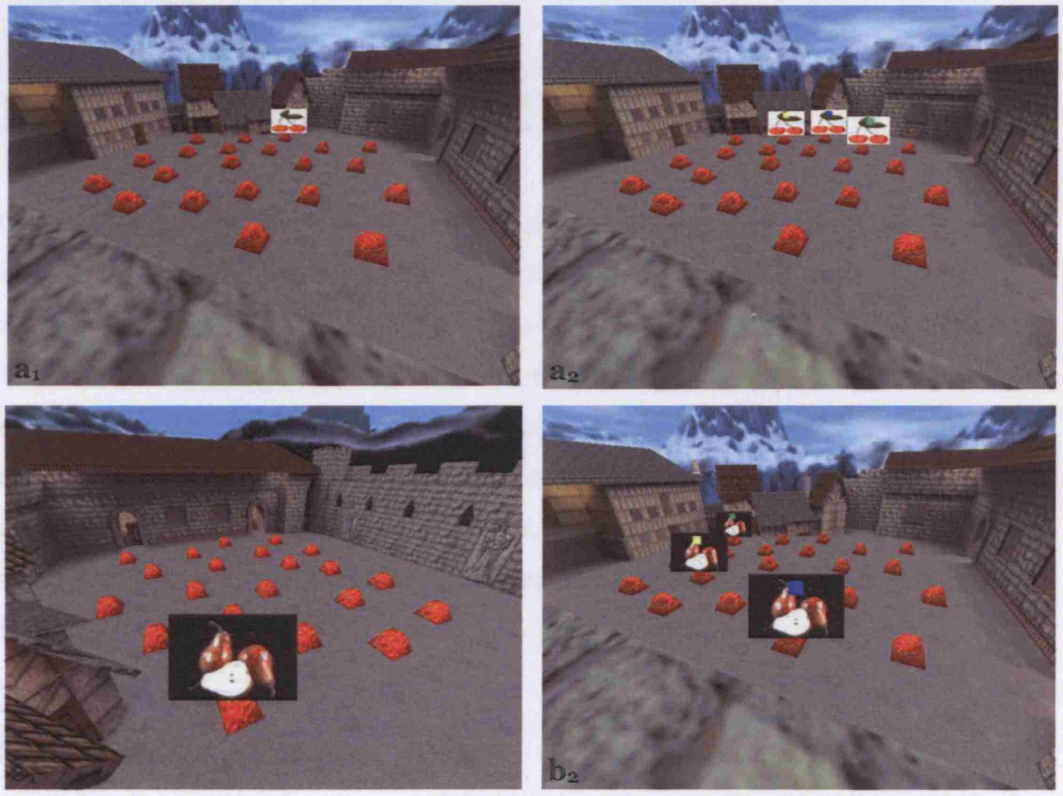


Figure 3.5 Experiment 1& 2 Snapshots from the modified courtyard experiment with 3 foil objects at testing. **a1** Presentation of an object from one view point. **a2** Testing for an item from the same view point. Note that foil objects appear close to the target. **b1&2** Presentation and testing in the shifted view, in which foils appeared on random locations excluding those adjacent to the target location.

Several different combinations of list lengths and numbers of foils were tested. The participants performed 3 sets each of same- and shifted view conditions at list length 3 with 3 and 4 foils at testing, and at list length 4 with 2, 3 and 4 foils.

Results

	List length = 3		List length = 4	
Number of foils	**shifted view**	**same view**	**shifted view**	**same view**
2			79.2% (40.6%)	80.3% (39.8%)
3	75.4% (43.1%)	85.5% (35.2%)	77.5% (41.8%)	82.9% (37.3%)
4	78.7% (41.0%)	80.4% (39.7%)	72.0% (45.0%)	84.8% (36.0%)

Table 3.1 Experiment 1 (close foils were used for the same view condition): Average performance in the same view- and the shifted view condition per number of foils and list length. N=18, standard deviations are shown in brackets.

Table 3.1 shows the results for all different combinations of list lengths and numbers of foils. Whereas across all combinations of list length and number of foils, the difference between the same view and the shifted view condition was still significant (ANOVA, $F_{(1)}=6.72$, $p<0.05$), and there is a significant interaction between combination of list length and number of foils and viewpoint change (ANOVA, $F_{(4)}=3.89$, $p<0.01$), two combinations of list length and number of foils yielded equivalent average performances in both the same- and shifted view conditions, list length 4 with 2 foils at testing, and list length 3 with 4 foils. This is further illustrated in the plot of average difference between the same and shifted view (see Fig. 3.6).

Discussion

The manipulation of the distance between the foil location, based on a discovered correlation between performance and foil distance in the pilot data, did result in the same view condition approaching a difficulty level equivalent to the shifted view, for two combinations of foil number and list length, if not across all combinations. One reason for the persistent difference in difficulty over-all could lie in the possibility that normal subjects can use both, egocentric and allocentric representations to solve the same view task. We will return to this argument in the general discussion of this chapter.

However, the outcome of equivalent performance averages for two of the combinations of foil number and list length was satisfactory with regard to the goal to apply the test to patient Jon, which will be described in experiment 2.

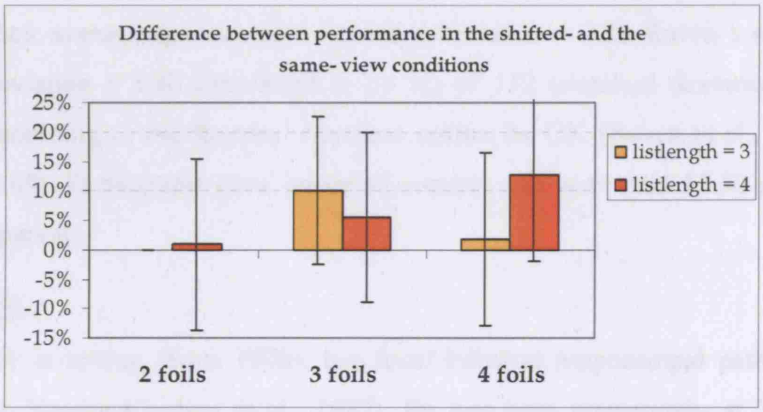


Figure 3.6 Experiment 1(close foils were used for the same view condition): Average difference between the shifted view and the same view condition per number of foils and list length. N=18, error bars indicate one standard deviation. The difference is close to zero for list length 4 with 2 foils and for list length 3 with 4 foils.

Experiment 2: Patient Jon's performance on the performance-matched courtyard experiment

In experiment 1 it had been found that if the foil locations at test were manipulated to be very close to the target location, then the performance between the same and shifted view was equivalent for normal subjects, for two combinations of number of foils and list length. Of these two combinations, list length 4 with 2 foils at testing, and list length 3 with 4 foils, the one with the higher number of foils was chosen for experiment 2, as chance performance for this version of the task was lower. In experiment 2, a patient with focal hippocampal pathology, Jon, is tested and compared with a group of age- and IQ-matched control subjects. It is hypothesised that whereas control subjects show an equivalent level performance in the same- and shifted-view conditions, patient Jon will perform similar to control subjects in the same view condition, that can be solved using an egocentric spatial representation, but will perform significantly worse than control

subjects in the shifted view condition, which requires an allocentric spatial representation.

Control subjects

13 male subjects (6 from experiment 1) took part as control participants for comparison with patient Jon. They were matched for age and IQ as assessed by the Raven's matrices. Their average age was 23.4 (standard deviation = 2.2), Raven's score of 10.2 (standard deviation = 0.8) equivalent to an IQ of 112 (standard deviation = 9.2) as estimated according to the Ravens' Matrices norms for UK (Raven et al., 1994, table APM XII p.69). Participants gave informed consent and were paid £7.50 per hour for their participation.

Patient Jon:

Jon, aged 24 at testing (born 1978), has focal bilateral hippocampal pathology (first described by Vargha-Khadem et al., 1997). He was born prematurely at 26 weeks of gestation, weighing less than 1 kg and suffering from breathing problems (Gadian et al., 2000). During his first six weeks of life he suffered from severe apnoea for prolonged periods, requiring intubation and positive pressure ventilation. He subsequently showed steady improvement and normal development. He was between 5 and 6 years old when it was discovered that he was experiencing spatial, temporal and episodic memory problems (i.e. difficulties in reliably finding his way, forgetting locations of objects, finding it hard to keep even regularly scheduled appointments, remembering details of everyday activities such as conversations or television programmes watched,...).

Clinical investigation revealed selective bilateral hippocampal pathology apparently caused by perinatal anoxia. His hippocampal volumes are approximately half those of control subjects. This brain abnormality was also the only one structurally visible although in a study together with other patients of similar aetiology (Gadian et al., 2000) quantitative MR techniques suggested the presence of more subtle pathology in other regions including the putamen bilaterally, the ventral part of the thalamus and the midbrain. There is evidence that the remaining hippocampal tissue is compromised but that extrahippocampal regions are largely preserved.

Jon's educational record suggests few problems with general knowledge acquisition (or 'semantic memory'), reflected in his GCSE in History. His verbal IQ was assessed to be 108 and his performance IQ 120 when tested at the age of 19. His full scale IQ was 114. Baddeley et al. (2001), who ran an extensive neuropsychological battery on Jon, conclude that, apart from poor spelling, Jon has above-average intelligence and performs normally on scholastic and language tests. Further, his executive capacities appear to be within the normal range. This starkly contrasts with his impaired performance on standard neuropsychological tests of everyday memory and recollection (Extended Rivermead Behavioural Memory Test, Wilson et al., 1999, Complex Rey Figure). Jon shows subtle sparing of Auditory Verbal Learning that can however be explained with an abnormal reliance on the recency effect (Greene et al., 1996), a *short-term* memory strategy that tends to be preserved in amnesia (Baddeley & Warrington, 1970). Also, Baddeley et al. (2001) showed, using the 'Doors & People' task of matched verbal and visual recognition and recall, that while Jon's recall performance was severely impaired, his recognition was spared in both modalities. This is congruent with his intact performance of purely familiarity-based recognition in a test of event memory, as will be discussed in Part II of this thesis.

Procedure

The procedure was as described in the pilot experiment. The experiment was changed as described in experiment 1, in that the foils for the same view condition appeared by the plinths closest to the target location, and on any but the nearest 5 neighbours to the target plinth for the shifted view condition. Further, the target objects appeared further away from the viewer in the same view condition and in random locations in the shifted view condition. Participants were given 4 sets of list length 3 with 4 foils at testing in both, the same and shifted view condition.

Results

Patient Jon showed marginally better performance in the same view and much worse performance in the shifted view condition, compared to 13 age- and IQ-matched male controls, see Fig. 3.7a). Figure 3.7b) shows the difference in performance between the shifted view and the same view for Jon and the controls, revealing Jon's significant impairment (z-score = 2.30).

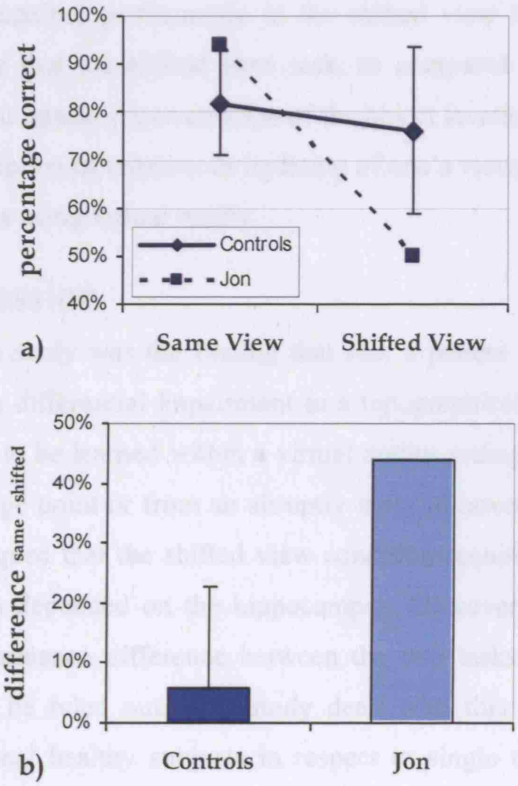


Figure 3.7 Experiment 2 (close foils were used for the same view condition)**:** Performance of patient Jon compared to 13 male age- and IQ-matched control subjects. List length was 3 and four foils were used at test. **a)** Average performance, error bars show one standard deviation. The control subjects perform equally in both conditions whereas Jon performs slightly better than controls in the same view condition but much worse in the shifted view condition. **b)** Difference of performance between shifted and same view (error bar shows one standard deviation). The difference between the two conditions is significantly higher for Jon. (King et al. 2004)

Discussion

The modified version of the original experiment (King et al., 2002), using foil locations close together for the same view test but not for the shifted view test condition, led to the control subjects not showing a differential result in the two conditions. By contrast, a patient with hippocampal pathology performed slightly better than controls in the same view condition but significantly worse in the shifted view condition. Thus, it can be excluded that the patient's performance difference is due to a difference in difficulty. We ascribe Jon's impaired performance in the shifted view task to his hippocampal pathology and argue that the shifted view task, as compared to the same view task, requires an allocentric spatial representation of the object locations to be learned. This is imposed by the disruption of continuous updating of one's viewpoint between study and test, as made possible using virtual reality.

General Discussion

At the outset of this study was the finding that Jon, a patient with focal hippocampal pathology, showed a differential impairment in a topographical memory task in which object locations had to be learned within a virtual reality setting, and were tested either from the same vantage point or from an abruptly induced novel vantage point (King et al., 2002). It was argued that the shifted view condition required an allocentric spatial representation which depended on the hippocampus. However, since healthy controls also showed a performance difference between the two tasks, a non-linear effect of difficulty could not be ruled out. This study dealt with this shortcoming, analysing performance of normal healthy subjects in respect to single trials and discovering a relationship between difficulty and the distance of foil locations at test. The foil locations were thus manipulated to occur close to the target location for the same view condition and further away in the different view condition. Upon this modification, in experiment 1 we found experimental conditions in which normal healthy subjects showed equivalent performance for both the same and different view conditions albeit the overall difference between same and shifted view condition persisted. Such conditions were subsequently used in experiment 2 to test patient Jon again. The findings and their implications are subsequently discussed.

A hippocampal patient's impairment on an allocentric spatial memory task, compared to one that can be solved using an egocentric spatial representation, is not due to a difference in difficulty

In experiment 2 we demonstrated that a patient with focal hippocampal pathology showed slightly but not significantly better performance than control subjects in a topographical memory experiment when tested on learnt object locations from the same viewpoint. By contrast, he showed impaired performance when tested from an abruptly induced novel viewpoint. Control subjects by comparison showed no significant difference between the same and shifted view condition. As hypothesised before (King et al., 2002), Jon's selective impairment in the shifted view condition is thought to be due to hippocampal dependence of the task that requires an allocentric spatial representation of object locations. This is in line with notable evidence for hippocampal involvement in allocentric spatial representations in humans (e.g. Abrahams et al., 1997; Ekström et al., 2003; Ghaem et al., 1997; Hartley et al., 2003; Maguire et al., 1998a; Spiers et al., 2001a) and other animals (e.g. Morris et al., 1982; O'Keefe & Nadel, 1978). Additionally, on the basis of control subjects performing similar to Jon in the same view condition but not differently in the same compared to the shifted view condition, we can rule out that Jon's impairment in the shifted view condition is difficulty-related.

Advantage of allocentric over egocentric strategy in terms of capacity

We note that despite manipulations that render the same view task harder for control subjects in order to adjust difficulty levels between the same and shifted view task of our topographical memory experiment, over-all the difference persisted, see experiment 1. As argued in the discussion of experiment 1, this could be due to the fact that control subjects could employ an allocentric representation even in the same view condition. Whereas in the current study using a list length of three items, Jon showed no impairment as compared to the controls in the same view condition, which is in line with his intact performance in recognising topographical scenes when test items were identical at test as at learning (Spiers et al., 2001a), it has been found previously, that Jon's performance in the same view task deteriorates at longer list lengths (King et al., 2002). An allocentric representation in the same view condition would allow an

integrated representation as compared to single egocentric representations that cannot be merged. This could result in an advantage in terms of storage capacity for the allocentric representation. The pattern of performance of hippocampal patient Y.R. in Holdstock et al.'s (2000) experiment further fits into this picture: Topographical memory was tested in darkness in the 'egocentric' condition, while the 'allocentric' condition involved moving between presentation and test. Albeit it would have been possible to maintain a continually updated egocentric representation in the latter condition, as discussed in the Introduction to Part II (Chapter 2), patient Y.R. showed a marginally greater impairment for this condition. More specifically, the difference between the two conditions was significant for the 60s delay but not for the 5s delay. Thus, it seems as if for shorter delays, the single-object representation formed could be maintained in the egocentric framework, but for longer delays, this strategy was deficient. In summary, both increasing the number of successively presented locations to be represented, and increasingly long delays between encoding and retrieval, appear to put the egocentric representation system at the edge of its capacities and hence promote the use of an allocentric representation, if available.

Conclusion

The shifted view task of a topographical memory experiment using a virtual reality paradigm, in which learned object locations are tested from an abruptly introduced novel viewpoint, requires an allocentric spatial representation and is hippocampal-dependent.

Chapter 4) Egocentric versus allocentric spatial representations in a patient with topographical disorientation and questionable dementia

Introduction

This study, published in Burgess et al. (2005), presents the case of a patient, C.F., who reported to the neurological hospital with topographical memory problems and word finding difficulties. Individuals who report with isolated symptomatic memory problems but as yet reasonably spared daily functioning have been diagnosed with 'clinically questionable dementia' or 'mild cognitive impairment' (Petersen et al., 1999) and it has been shown that they have an increased probability to develop Alzheimer's disease compared to the normal population (Fowler et al., 2002; Petersen et al., 1999). In Alzheimer's disease, structural changes are known to affect hippocampal functioning as one of the first, hence the correlation with memory problems. However, as discussed in the General Introduction (Chapter 1), not all memory function is hippocampal-dependent. In the diagnosis of 'clinically questionable dementia' or 'mild cognitive impairment' a memory test would be useful that is demonstrably hippocampal-sensitive. We tested patient C.F. on the topographical memory test developed in Chapter 3 that, using a virtual reality paradigm, probes memory for object locations either from the same view or from an abruptly introduced different viewpoint, and has been demonstrated to be sensitive to hippocampal damage (King et al., 2002; 2004). Additionally, her performance on another virtual reality test of spatial memory (as used in Spiers et al., 2001a) was also compared to a group of age- and IQ-matched control participants, with the attempt to experimentally capture her reported daily wayfinding difficulties. The assessment was completed by a series of other neuropsychological tests.

As discussed in the Introduction to Part I (Chapter 2), spatial memory and other spatial processing abilities have been shown to decline in normal healthy ageing (e.g. Driscoll et al., 2005; Inagaki et al., 2002; Monacelli et al., 2003). Moreover, findings from Driscoll et al. (2005) and Monacelli et al. (2003) suggest that *allocentric* spatial orientation decreases selectively compared to egocentric spatial orientation. Thus, the

topographical memory experiment developed in Chapter 3, used for testing patient Jon, aged 24, may yield different patterns of performance in elderly subjects (the incidence of mild cognitive impairment increases around the age of 65). In a first step to meet this consideration, the parameters of the experiment (list length and number of foils) were adapted in an attempt to make the test less taxing for the elder participant group. This adapted version of the experiment was used to test a group of elderly participants and to assess patient C.F. whose performance was compared to a subgroup of age- and IQ-matched control participants from the elderly participants group.

Methods

Normal elderly participants:

15 subjects, 9 female and 6 male, aged 63 years on average (ranging from 57 to 71), gave written consent to participate in this experiment and were paid £7.50 per hour for taking part. Their Raven's score was 9.7 of 10 (standard deviation = 2.1) which refers to an IQ of about 118 in that age group, according to the Ravens' Matrices norms for UK (Raven et al., 1994, table APM XII p.69). All participants were also tested on scene recognition (Warrington, 1996), average score = 27.2 of 30 (stdev = 2.0), and on the Little Man Test of mental rotation (Ratcliff, 1979), average score = 28.9 of 32 (stdev = 5.1).

Patient C.F.

A female, 65 year old, right-handed writer first referred to Dr. Kennedy in 2002 for evaluation of progressive topographical memory and word finding difficulties. At the time of assessment, the patient's husband reported that despite having previously known part of London very well, in the last year she had got lost on occasion and she had also become very vague about how to get from one place to another. He also noted that she became unable to understand the relationships among very familiar locations.

Neuropsychological assessment of other than memory abilities:

Patient C.F.'s verbal IQ was in the very superior range, and the performance IQ in the superior range (Verbal IQ=132, Performance IQ = 124 as assessed by the revised Wechsler Adult Intelligence scale, 1986). She presented with slight word finding difficulties as assessed on the graded naming test (McKenna & Warrington, 1983), where her performance was effortful although within the average range. Her

performance was entirely normal on a wide range of other cognitive abilities tests, such as literacy, calculation skills, speed and attention, visual object and space perception, and on tests tapping into frontal lobe dysfunction. On two further spatial tests of mental rotation, namely the flags test and the Little Man Test (Ratcliff, 1979), she was also unimpaired (see comparison with control subjects in Table 4.1. A brain MRI scan contemporaneous with experimental investigation showed no visible signs of pathology.

Neuropsychological memory investigation:

When questioned by a neuropsychologist about her memory difficulties, the patient spontaneously reported that she had difficulty orienting herself even in familiar surroundings, however she had no problem recognising the buildings. Her difficulties are exemplified by her inability to describe for example the route to one of her local restaurants where she used to dine regularly over the past years.

Verbal recognition memory was in the lower normal range, whereas recognition memory for faces was impaired (verbal recognition : 41/50, 25-50th %ile, face recognition: 36/50, 5-10th %ile, tests from Warrington, 1984). Performance on naming and recognising famous faces was also weak (35/50, 5th %ile). On the other hand, she showed normal, slightly above average verbal recall memory (immediate recall: 49/56, >90%ile, delayed recall: 24/24, >90%ile). She also showed good performance on a test of outdoor scenes recognition (24/30, 50-75th %ile, test from Warrington, 1996), see also below for direct comparison with control subjects. Further she was unimpaired on a recognition test for unknown buildings and landscapes (buildings: 41/50, landscapes: 42/50), as compared to approximately matching control subjects from another study (buildings: mean = 42.4, standard deviation = 3.3, landscapes: mean = 43.5, standard deviation = 5.0, see Cipolotti & Maguire, 2003). Finally, she showed well preserved memory for "semantic topographical memory" i.e. for recognising familiar (London and world) landmarks (Cipolotti, 2000; see McKenna & Warrington, 1978).

A clinical diagnosis of possible very early Alzheimer's Dementia was made on the basis of the above neuropsychological testing.

Control participants for comparison with patient C.F.

Five normal healthy women of the above normal elderly participants pool, matched patient C.F. in age (60 years, range = 57-64 years), education (to degree level) and IQ, about 124 as derived from a Raven's average score of 10.8 out of 12, stdev. = 1.2 (Raven's Matrices norms for UK, 1994, table APM XII p.69). Their results on Warrington's (1996) test of scene recognition and the Little Man test of mental rotation (Ratcliff, 1979) are displayed in Table 4.1.

	Patient C.F.	Control Subjects
Scene Recognition Test (Warrington, 1996)	24/30 ~50th -75th %tile	mean: 27.4/ 30 (stdev.:0.9)
Little Man Test (Ratcliff, 1979)	29/32	mean: 28 /32 (stdev.: 5.9)

Table 4.1 Comparison between patient's and control subjects' scores on two additional neuropsychological tests. The patient performs within the normal range on both tests, scene recognition and mental rotation.

Procedure of the topographical memory test

The subjects were presented with a virtual environment as used in Chapter 3 (see also King et al., 2002; King et al., 2004). Taking a first person's perspective subjects looked down onto a virtual courtyard from rooftops. In each trial the subject appeared in one corner on the rooftop and walked to one side of the square, as indicated by a marker. From there presentation of a list of items (one, two, or three, each presented for 3s, separated by 1s) on plinths down in the courtyard preceded a test of those item's locations 5s later. Testing occurred either from the same viewpoint, or an abruptly introduced shifted view, from the opposite corner above the courtyard. Subjects indicated by key press, which of the three presented copies was in the same location as the item at presentation. An illustration of the subjects' view into the courtyard at presentation and test is shown in Fig.3.5 (Chapter 3). Participants completed 8 trials of each list length, and were tested on the same and shifted view conditions for a total of 96 responses from 48 trials of randomly interleaved types. This procedure is the same as

used in experiment 2 of Chapter 3: Foil object locations for the same view condition appeared by the plinths closest to the target location, and on any but the nearest 5 neighbours to the target plinth for the shifted view condition. Also, the target objects appeared further away from the viewer in the same view condition and in random locations in the shifted view condition. However, hoping to approximately match difficulty for the older participants we chose shorter list lengths, see above.

Figure 4.1 Lego model of the virtual reality courtyard environment.

Test instruction by means of a Lego model

To ensure that subjects understood the virtual environment and were aware of the feature of automatic change of virtual location in the shifted view condition, we explained the procedure of the experiment using a model of the virtual courtyard environment, rebuilt in Lego carefully true to detail, see Fig. 4.1). In the instruction, particularly the difference between the two vantage points was stressed.

Procedure of the virtual reality navigation task (see also Spiers et al., 2001a):

A virtual reality environment, programmed by Neil Burgess using the commercially available video game Duke Nukem 3D incl. editor (3D Realms Entertainment; Apogee Software), was presented on a 17-inch computer screen (refresh rate 21Hz). The virtual environment consists of a small group of functionally distinct buildings such as a cinema, a bookshop, and so on, arranged around a crossroad (see Fig. 4.2). Participants explored the town using the arrow keys of a normal keyboard until they had inspected all parts of the town at length and felt they knew where everything was. This lasted approximately 15 minutes. Their task was then to find the way to a target location (a

picture of which was constantly displayed on a piece of paper next to the screen as they travelled) by the shortest possible route from a given start location. If they failed to find a location after 4 minutes they were guided to it and from there the next location was probed. This task was performed by patient C.F. and the four control subjects described in the above section.

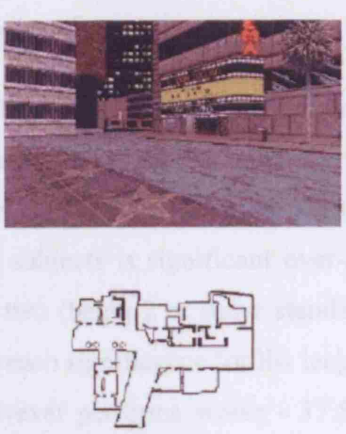


Figure 4.2 The virtual environment of the navigation task on which patient C.F. and 4 female control subjects were additionally tested. A: View of the crossroads with the cinema on the right. B: Aerial perspective of the virtual town layout which was not shown to subjects. (from Spiers et al. 2001a)

Results

Performance of normal elderly participants

The reduction of list length and number of foils for elderly participants as compared to the parameters used for subjects in their twenties in Chapter 3 led to the following result: Performance in the elderly population was significantly lower in the shifted view condition compared to the same view condition, see Fig. 4.3, unlike the matched performance that we had found for the younger population, see Chapter 3. The over-all effect of list length ($F_{1,13}$=26.34, $p<0.001$) and of condition ($F_{2,26}$=9.09, $p=0.001$) was significant, whereas the interaction wasn't ($F_{2,26}$=1.21, $p=0.316$). The performance significantly declined from list length 1 to the other list lengths (paired one-tailed t-tests, $p<0.01$, $p<0.001$) in the same view condition and was significantly lower between list length 1 and 3 (paired one-tailed t-test $p<0.05$) and 2 and 3 (paired one-tailed t-test, $p<0.01$) in the different view condition.

Figure 4.3 Average performance in the topographical memory experiment of 15 normal elderly participants (9f, 6m, mean age=63), over list lengths (foil number = 3 throughout). Performance declines for larger lists and is significantly worse for the shifted as compared to the same view condition.

Performance of Patient C.F. compared to five age- and IQ matched control subjects

The patient's performance does not differ from that of the control subjects in the same view condition at all three list lengths, see Fig. 4.4. This finding sharply contrasts with her decreased performance in the shifted view condition. The difference in the shifted view performance between patient C.F. and the control subjects is significant over-all and reaches significance for single list lengths one and two (being 2 or more standard deviations lower), see Fig. 4.4. (The difference does not reach significance for list length 3 due to one poor performing control. Patient C.F. however performs worse - 37.5% correct - than this participant - 41.7% correct - in this condition.).

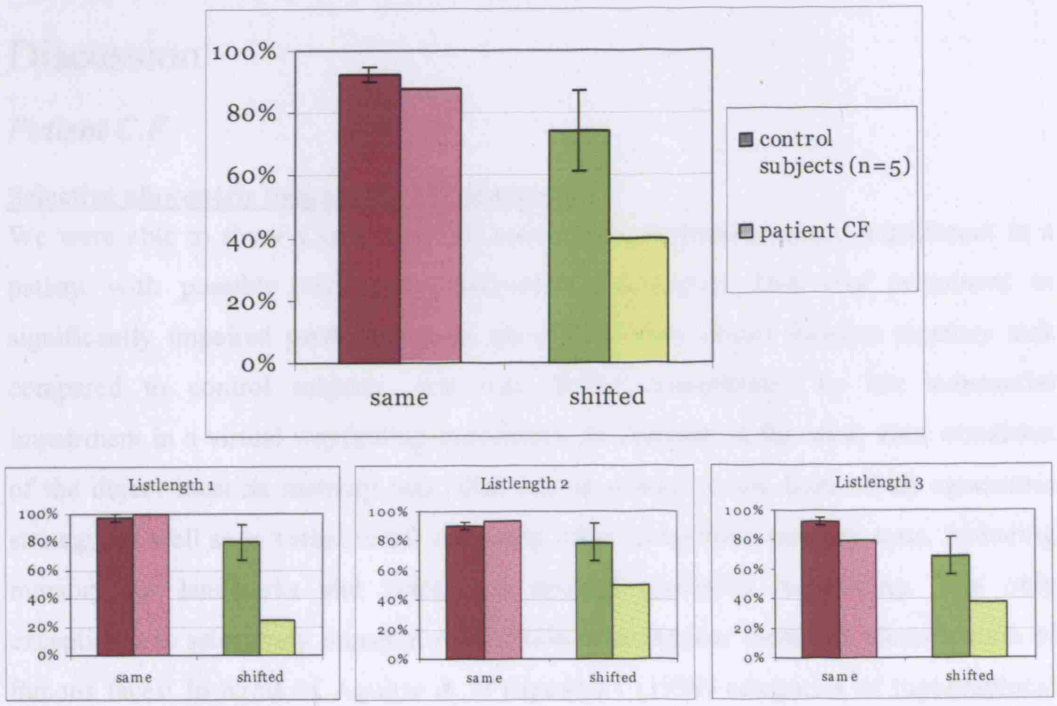


Figure 4.4 Average performance of 5 age- and IQ-matched female control participants and patient C.F. in the same and shifted view condition, over-all and per list length. The difference in the shifted view performance between patient C.F. and the control subjects is significant over-all and for single list lengths one and two.

Results from the Virtual Reality Navigation Task

Whereas the patient did not differ from the control subjects on the basis of her navigation speed per se, she failed to find 4 of the 10 locations within the 4 minutes limit, while none of the control subjects failed any location.

Additionally, the paths taken to the locations the patient was able to find were significantly longer than the control subjects' - average path length was 200 for patient C.F. compared to 123 (standard deviation = 25) in the control group - and deviated from the control subjects' routes qualitatively in that they included several visits to wrong locations, and repeated failures to make a correct turn at a junction. They were accompanied by patient C.F.'s self-confessed lack of any sense of the direction in which the target location might lie.

Discussion

Patient C.F.

Selective allocentric topographical impairment

We were able to show a selective, *allocentric* topographical memory impairment in a patient with possible very early Alzheimer's dementia. This was prominent in significantly impaired performance on the shifted view object location memory task compared to control subjects, and was further corroborated by her substantial impairment in a virtual wayfinding experiment. In contrast, in the same view condition of the object location memory task, that can be solved on the basis of an egocentric strategy, as well as in verbal recall and many other recognition memory tests, including memory for landmarks and maps, she showed preserved functioning. The only exception was selectively impaired recognition of unfamiliar faces and identification of famous faces. In terms of Aguirre & D'Esposito's (1999) categories of topographical disorientation we could show that the patient's impairment is not in the egocentric domain and that her landmark recognition is intact. Moreover, the patient's intact landmark recognition but impaired face recognition lends further evidence to Aguirre & D'Esposito's (1999) hypothesis that the two functions are supported by separate if neighbouring neural processes. Patient C.F.'s impaired face recognition is suggestive of

damage to the fusiform gyrus (Kanwisher et al. 1997; Wada & Yamamoto, 2001; see also Chapter 9).

As the patient does show impaired learning of novel environments, she could tentatively be classified as presenting with 'anterograde disorientation'. Also, given her wayfinding impairment, 'heading disorientation' could also apply. However, on the basis of results on this test from a patient with focal hippocampal pathology, Jon (King et al., 2002; King et al., 2004, see Chapter 3), we are aware of the probability that her deficit might be caused by early hippocampal pathology and not retrosplenial pathology, as would be suggested by 'heading disorientation', or parahippocampal pathology, as Aguirre & D'Esposito (1999) suggested would underlie 'anterograde disorientation'. Note, however, that Turriziani et al. (2003) did suggest hippocampal pathology to underlie anterograde disorientation. Also, these areas entertain strong reciprocal connections, and thus, impairment in one area might lead to disruption of functioning in another.

Subtle hippocampal impairment could point to early onset of Alzheimer's disease with underlying pathology in the transentorhinal region (Braak & Braak, 1991), so early that the structural brain analysis would not yet reveal any visible change. It has been argued before that specific memory deficits might indeed precede apparent structural changes by years (Fox et al., 1998).

Verbal versus spatial memory deficits

Remarkably, patient C.F., a professional writer, shows intact verbal recall. This stands in contrast to both patient Jon's severe verbal recall impairment and the long established hippocampal involvement in verbal recall memory (e.g. Frisk & Milner, 1990; Milner, 1971; Seidenberg et al., 1993). Further, delayed recall of verbal material has been reported to be severely impaired in Alzheimer's disease from an early stage (Greene et al., 1996; Hodges & Patterson, 1995). It might be that patient C.F.'s verbal functions were higher than average prior to the onset of her illness, reflected in her above average verbal IQ, and this may conceal any effect of hippocampal malfunction on verbal memory as yet. Or her dissociation between spared verbal recall and impaired allocentric topographical memory, if subsequently found to depend on spared left and

impaired right hippocampal functioning, might be intriguing evidence for the lateralisation of hippocampal memory function (verbal on the left and spatial on the right), as postulated in the Cognitive Map theory (O'Keefe & Nadel, 1978). Until structural evidence can be provided to decide upon this, support to strengthen this hypothesis comes from the comparison of patient C.F.'s clinical picture with that of a patient with semantic dementia reported by Maguire & Cipolotti (1998) who shows the contrasting pattern of a wide ranging verbal memory impairment in the face of intact spatial recognition and route learning abilities. Her pathology involved predominantly the left temporal lobe. The further discussion of lateralised hippocampal function is resumed in the General Discussion (Chapter 12).

Next I discuss the performance of the normal elderly subjects in the two conditions (egocentric versus allocentric) of the topographical memory experiment:

Performance of normal elderly subjects

Whereas patient C.F., like patient Jon (King et al., 2002; King et al., 2004), showed differential performance between the allocentric and egocentric memory condition of the topographical memory experiment, the performance of healthy elderly participants was also significantly different. By contrast, the task yielded equivalent performance in the two conditions in a younger population, see Chapter 3 and King et al. (2004). This lends further evidence to the hypothesis that allocentric spatial memory function might decline selectively in normal ageing as recently corroborated by results from a virtual Morris watermaze task (Driscoll et al., 2005) and other allocentric spatial tasks (Inagaki et al., 2002; Monacelli et al., 2003).

Alternatively, as discussed in Chapter 3, the same view condition of our topographical memory experiment might be likely to yield better performance in unimpaired participants because they can make use of an allocentric strategy in addition to the egocentric strategy whereas in the other condition they are restricted to the allocentric strategy only. However, as demonstrated in Chapter 3, difficulty could be matched for the younger population and only on that basis were we able to exclude that the difference between a hippocampal patient and control subjects was due to difficulty and

argue instead that the differential performance was grounded in an allocentric spatial memory impairment caused by hippocampal damage. Thus, in order for the test to be used to assess (early) hippocampal dysfunction, the attempt remains to match the two conditions for difficulty. This endeavour forms the basis of the investigations in Chapter 5.

Chapter 5) A test for Alzheimer's disease in people with Mild Cognitive Impairment

Introduction

A topographical memory experiment that we developed using virtual reality successfully discriminated between intact egocentric spatial representations and impaired allocentric spatial representations in a patient with focal hippocampal lesions, (see Chapter 3 and King et al., 2002; 2004). Moreover, it could be excluded that this differential impairment was due to a difficulty difference between the two conditions, same view (only affording an egocentric representation) and shifted view (relying on an allocentric representation). This had been shown on the basis of equivalent performance of healthy subjects in the two conditions (see Chapter 3 and King et al., 2004). Such a test, highly sensitive to intact hippocampal functioning, would be of use in the assessment of early Alzheimer's disease where neural pathology in the transentorhinal region (a neural information passage to and from the hippocampus) marks the onset (Braak & Braak, 1991). Typically, memory problems are the earliest symptoms reported in people who later develop Alzheimer's disease. Such cognitive deficits precede apparent structural changes by years (Fox et al., 1998). Individuals who report with isolated symptomatic memory problems but as yet reasonably spared daily functioning have been diagnosed with 'clinically questionable dementia' or 'mild cognitive impairment' (Petersen et al., 1999). Recent studies have tried to identify individuals with early signs of developing Alzheimer's in this high-risk population (Fowler et al. 2002; Fox et al., 1998; Swainson et al. 2001). This is all the more imperative as therapeutic agents for the symptomatic treatment of Alzheimer's disease have been discovered recently, and as therapeutic options to reverse, slow or halt progression of Alzheimer's disease are being investigated (Fowler et al., 2002). However, the memory tests currently used suffer from a lack of discrimination between hippocampal and non-hippocampal memory function, as discussed in the Introduction to Part I (Chapter 2). This is where our test attempts to fill a gap.

Chapter 5

As shown in Chapter 4, there is a difficulty involved in using our test for an elderly population (the incidence of mild cognitive impairment increases around the age of 65). In Chapter 4 the test that yielded equivalent performance in both conditions in a younger population (aged 23 in average), see Chapter 3 and King et al. (2004), showed a significant difference between the two conditions in a group of elderly participants (aged 63 in average). This is in line with recent evidence that allocentric spatial memory and other allocentric spatial skills might deteriorate selectively in normal ageing (Driscoll et al., 2005; Inagaki et al., 2002; Monacelli et al., 2003). In Chapter 4 shorter list lengths and lower numbers of foils had been used to make the test less taxing for an elderly population. More extensive adaptations appear necessary to achieve difficulty match in this population. Neurologists interested in using the test additionally expressed the preference for a non-computerised test. It was decided to abandon the original virtual reality paradigm and work with a lego model. Note that the abrupt switch of viewpoint in the virtual reality environment is the crucial feature of the test to ensure no egocentric strategy is sufficient to solve the task. This might exactly be why elderly subjects found the task hard.

In the new version of the task, the same view condition was instantiated by presenting and subsequently testing object locations within a miniature environment built in lego. The shifted view additionally involved a rotation of the environment between presentation and test. We have argued in the Introduction to Part I (Chapter 2) that rotating an array may still promote an allocentric representation as compared to (physically or mentally) rotating around an array which might be solved on the basis of a continuously updated egocentric representation (Burgess et al., 2004; Nardini et al., 2005; Wang & Simons, 1999). The test development is described in detail in experiment 1. Further, it was possible to assess patient Jon on this test. This allowed a first validation of the two test conditions with respect to hippocampal affordance. Next, a group of elder hippocampal patients was also tested on this paper and pencil (and lego) version of the topographical memory experiment, see experiment 2.

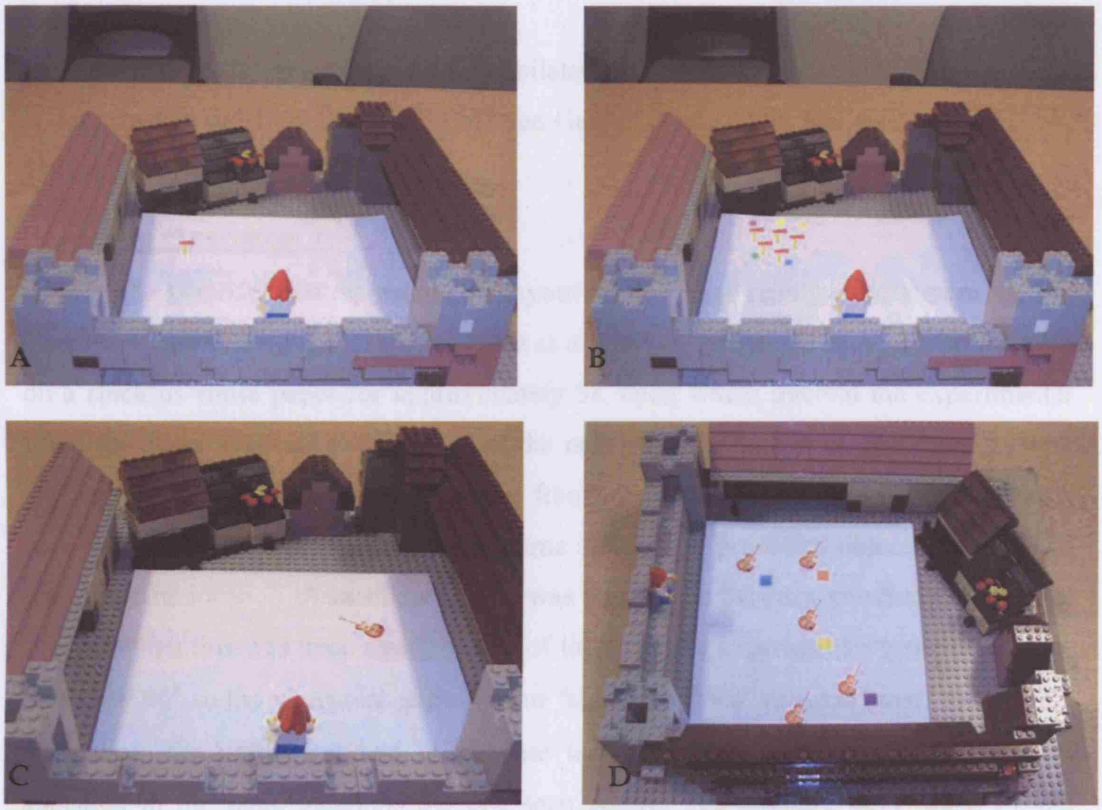


Figure 5.1 Illustration of the legotown experiment. **A** and **C** Presentation from the "south" side. **B** Test in the same view task. **D** Test from the rotated view task. View now from the "east" side.

Experiment 1

Normal elderly participants

11 middle aged and older participants, of average age 65, ranging from 54 to 73, took part in this experiment. They all gave written consent and were paid £7.50 per hour for participation. They were all screened on a small range of neuropsychological tests: Their average Raven's score was 8.4 of 12 (standard deviation = 2.8) equivalent to an IQ of 112 (standard deviation = 32.2) as estimated according to the Raven' Matrices norms for UK (1994). They scored in average 27 of 30 (standard deviation = 3.4) on Warrington's scene recognition test (Warrington, 1996), 10 of 11(standard deviation = 1) on the flags test and 29.5 of 32 (standard deviation = 4.1) on the Little Man test (Ratcliff, 1979).

Patient Jon

Patient Jon, aged 24 at testing, has focal bilateral hippocampal pathology. His aetiology is described in detail in Chapter 3 (and see Gadian et al., 2000; Vargha-Khadem et al., 1997).

Procedure experiment 1

Within a lego-model that represents the layout of the virtual reality environment used in Chapter 3 and 4 (see Fig. 5.1), one object at a time was presented in a random location on a stack of white paper for approximately 3s, upon which interval the experimenter lifted the sheet to reveal the location of the next object. The participants were thereby looking at the courtyard lego-scene either from the "east"-side or from the "south"-side (see Fig. 5.1). They were instructed to name aloud each presented object and to try to remember its location. A cardboard sheet was interleaved between presentation and test sheets. When this was uncovered, in half of the trials the experimenter turned the lego-model by 90° so the viewpoint shifted from "south" to "east" or from "east" to "south". At testing, the participant had to indicate which of three colour-coded foil objects appeared in the same locations the one seen before. The answers were noted by the experimenter and later computerised. Participants completed 32 trials of each condition. The objects each occupied one of 32 possible random locations. Foil objects were evenly distributed on other random locations in the shifted view condition while placed close to the target location in the same view condition. This procedure mimics the one chosen in the computerised version presented in Chapter 3 and 4 and aimed at making the same view task harder so as to adjust difficulty levels between the same and shifted view condition.

Subjects were notified that the features of the lego surroundings were there to help remembering the correct locations of the objects. List length was two items for the group of healthy elderly participants, i.e. the locations of two subsequently presented objects were tested per trial. Patient Jon was given two blocks, one with list length 2, the other with list length 4.

Results experiment 1

The average performance of normal participants in the rotated view condition was "more than matched" compared to performance in the same view, i.e. significantly better (t-test, $p<0.01$), see Fig. 5.2. Presenting foil items very close to the target for testing object location in the same view led to performance in this task dropping below the usually more difficult shifted view task.

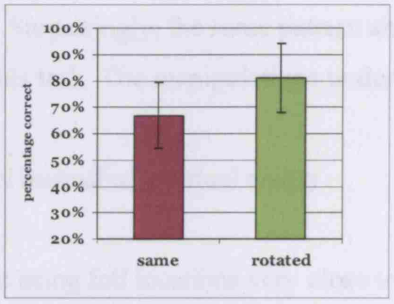


Figure 5.2 Experiment 1: Average performance of 11 normal elderly participants over the same and rotated view conditions (error bars show standard deviations). Subjects are significantly better in the rotated view condition.

Unexpectedly, patient Jon's pattern of results was inversed compared to his performance on the virtual reality version of the topographical memory experiment (see Chapter 3 and King et al., 2004) in that he was superior in the thought "allocentric" object location memory test from a different viewpoint compared to the test from the same view, even at an increased list length of 4 objects, see Table 5.1.

	condition	
list length	same view	rotated view
2 objects	**40%**	**85%**
4 objects	**35%**	**65%**

Table 5.1 Experiment 1: Patient Jon's scores (chance level is 20%). Note that he is better at the rotated view task compared to the same view task.

Discussion experiment 1

On the basis of results from Chapter 4 we had reasons to believe that elderly subjects found one condition of a topographical memory task more taxing than the other whereas young participants showed equivalent performance in both conditions, see Chapter 3 and King et al. (2004). Namely, the performance of the elderly in the shifted view condition affording an allocentric spatial representation was lower compared to the same view condition that could be solved using either an egocentric or an allocentric representation. The adaptation of this experiment, previously run using a virtual reality setting and here

presented using a lego model, succeeded in raising performance in the shifted view condition beyond that of the same view condition for elderly participants. Or rather, performance in the same view condition dropped. Surprisingly, the same pattern showed when a hippocampal patient, Jon, was tested on this task. The manipulations undertaken in experiment 1 involved:

a) presenting the test array using a lego model instead of a virtual reality environment
b) probing memory for object locations at test using foil locations very close to the target location in the same view condition.

The first measure had various consequences. These are further discussed in the general discussion below. The second measure might have made the same view condition too hard. Therefore, it was marginally changed for use in a group of elderly hippocampal patients and a group of age-matched control participants, as presented in experiment 2.

Experiment 2

Here I present three patients with medial temporal lobe pathology that were tested by Chris Bird on a slight alteration of experiment 1. It has been shown in experiment 1 that a paper and pencil version of the topographical memory experiment, comparing object location memory from the same and from a shifted viewpoint, yielded better performance in the formerly easier condition, the same view condition, both, in a group of elderly subjects and in patient Jon. On the basis of an item analysis on the data of experiment 1 some of the hardest trials were changed in an attempt to make the same view task easier again. Performance of the patients was compared to that of a group of healthy, age-matched control participants.

Elderly control participants

15 elderly subjects, 10 females and 5 males, average age = 74, ranging from 66 to 80, were tested by Chris Bird. Their Raven's score was 7.1 of 12 (standard deviation = 2.3), equivalent to an IQ of 110 (standard deviation = 26.5) as estimated according to the Ravens' Matrices norms for UK (Raven et al., 1994).

Medial temporal lobe patients tested in experiment 2

Chris Bird provided the case descriptions of the three patients tested:

Patient R.B., focus of pathology: bilateral hippocampal and amygdala

R.B. is a 57 year old, male, former market trader. Six months prior to the present investigation R.B. began to experience "panic attacks" manifested as episodes of anxiety, with no obvious triggers. The following month he continued to experience frequent daily panic attacks and began to notice some problems with episodic memory that rapidly became more severe. R.B. had severe problems navigating around familiar routes in his home city of London. General neurological examination was normal, although discussions relating to his symptoms would often precipitate a "panic attack". An MRI brain scan revealed abnormal high signal restricted to the hippocampi and amygdalae with no abnormality elsewhere in the temporal lobe. A neuropsychological assessment was carried out 2 months prior to the present investigation. Verbal and performance IQ was in the average range, which was considered to represent some degree of intellectual underfunctioning in view of his estimated high average premorbid IQ based upon educational level. Anterograde memory was found to be intact on most tests, although retrograde memory was impaired. He performed poorly on a verbal fluency test of executive functioning, although this may be confounded by the fact that English is his second language.

A diagnosis of autoimmune encephalitis associated with anti-voltage gated potassium channel (anti-VGKC) antibodies was made and subsequently confirmed. An overnight EEG telemetry confirmed that the "panic attacks" were partial seizures. R.B. underwent immunomodulatory therapy and pharmacological management of his partial seizures. This alleviated his symptoms, although when he took part in the present study, he still complained of topographical disorientation.

Patient E.F.: focus of pathology: right hippocampus

E.F. is a 58 year old, female, housewife. In 1996, she developed sudden onset tingling and weakness in the left arm. Subsequent to this event, she noticed an impairment in remembering events, appointments and conversations. She also began to notice a difficulty with her sense of direction particularly when walking in unfamiliar places.

Neurological examination was entirely normal. At the time of the present study E.F. claimed that her memory has improved although her husband still noted a mild topographical disorientation that is more pronounced in unfamiliar environments. Two recent MRI brain scans have identified atrophy involving the right hippocampus focally, with normal appearance of the fusiform and parahippocampal gyrus and the remainder of the temporal lobes. Neuropsychological assessments have revealed a static profile over the last two years. Verbal and performance IQ are both in the average range, consistent with estimates of premorbid ability. Language, visual perception and executive functions are all unimpaired. Verbal memory is also unimpaired. However, she performed poorly on tests of visual recall and a test of visual recognition. Given the sudden onset of her symptoms and her static neuropsychological profile, a vascular aetiology is suspected (ischemia).

Patient WF, focus of pathology: right medial temporal-occipital area

W.F. is a 70 year old male former airport terminal duty officer. In August 2000, he had a sudden onset of dizziness and mild weakness in his left arm. Subsequently he was disorientated and had difficulty walking as he started bumping into objects. A neurological examination revealed a right homonymous upper quadrantanopia. The only other neurological sign was a mild postural tremor. An MRI brain scan showed right sided occipital and temporal lobe infarction in the territory of the posterior cerebral artery. This affected the lingual and parahippocampal cortices and extended into posterior portions of the hippocampus. Following discharge, W.F. complained of difficulty in recognizing famous people's faces on television, although friends and family never presented a problem. He has experienced several episodes of topographical disorientation, although he is able to live independently. He was also concerned that his quadrantanopia was expanding although this was found not to be the case. A formal neuropsychological investigation found his verbal and performance IQ's to be in the average range which is broadly in keeping with premorbid estimates. High level visual perceptual deficits were also detected.

Procedure experiment 2

The procedure was as described in experiment 1 above, however, upon analysis of item difficulty, some of the hardest trials in the same view condition of experiment 1 were made easier by placing the foil objects further apart.

Results experiment 2

The slight modification from experiment 1 to experiment 2 resulted in equalising the difficulty between the same view and the rotated view condition for normal elderly subjects, see Fig. 5.3. By contrast, all medial temporal lobe patients show higher scores for the rotated view task compared to the same view task, see also Fig. 5.3.

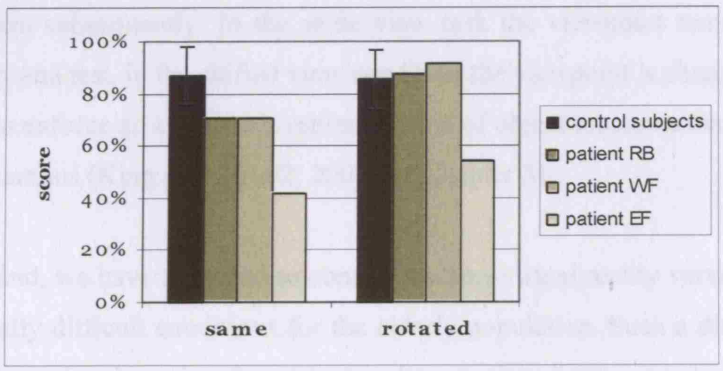


Figure 5.3 Experiment 2: Average performance of normal elderly control subjects and three temporal lobe patients in the same view and rotated view condition (error bars show standard deviations). Control subjects' performance does not differ between the conditions. All temporal lobe patients show worse performance in the same view condition compared to the different view condition.

Discussion experiment 2

On the one hand, the former over-correction of difficulty between the same view condition and the different view condition in the adapted topographical memory paradigm for testing elderly subjects has been corrected in experiment 2 compared to experiment 1. Normal healthy participants showed equivalent performance in the two tasks. However, the pattern of performance in hippocampal patients is still contrary to the expected. Whereas it was hypothesised that the shifted view condition but not the

same view condition would afford a spatial representation that is dependent on the hippocampus, as has been demonstrated in patient Jon, see Chapter 3 and King et al. (2002, 2004) using a virtual reality version of the task, here we saw that two of the three hippocampal patients performed at the same level as control participants in the shifted view condition but were impaired in the same view condition. Attempts to explain this phenomenon are made in the general discussion.

General Discussion

At the outset of this experiment was the attempt to adapt a topographical memory experiment involving virtual reality for use in an elderly population. The experiment consists of two different tasks that require participants to encode object locations and remember them subsequently. In the same view task the viewpoint remains the same between study and test, in the shifted view condition the viewpoint is changed which has been shown to enforce an allocentric representation of object locations that is dependent on the hippocampus (King et al., 2002; 2004 see Chapter 3).

On the one hand, we have managed to construct a non-virtual reality version of this test with two equally difficult conditions for the elderly population. Such a difficulty-match was achieved previously, using the virtual reality version, however only for a younger population (see Chapter 3 and King et al., 2004) whereas an older participants group showed significantly lower performance in the shifted view task (see Chapter 4). This is in line with other recent reports of a selective decrease of allocentric spatial memory performance with age (Driscoll et al., 2005; Inagaki et al., 2002; Monacelli et al., 2003). However, as shown here, once the parameters were adjusted sufficiently (mainly the distance between foil- and target location in the same view task at test), normal elderly participants performed equally in both conditions, see experiment 2.

On the other hand, the test had at the same time lost its previous hippocampal sensitivity, as demonstrated by patient Jon and three other medial temporal lobe patients showing an unexpected and reversed results pattern, performing better in the shifted-view condition than in the same-view condition.

How could this be explained?
Moving the experiment out of virtual reality had several consequences. (This measure had been taken in response to requests for a non-computerised version favoured in traditional clinical practise, but had also been thought to make the task easier for the elderly population.)

In the lego-version the change of viewing angle between presentation and test in the rotated view was smaller (90° compared to 140°). This might have rendered the rotated view task easier. In fact, King et al. (2002) had shown previously that patient Jon's performance decreased with increasing viewpoint shifts from 55° to 85° and 140°. His impairment was however significant also for the 85° condition.

Further, it is possible that the more distinct and salient features of the lego environment (as confirmed by reports from the control subjects) facilitated verbal encoding strategies at the low list lengths used (e.g. "the guitar under the brown roof and the football in front of the houses with the flowers"[1]), further enabled by longer exposure time compared to the automatically timed virtual reality experiment. Such additional strategies could be supported by (phonological) working memory function. It might have improved performance in both conditions but importantly, it might have made the rotated view condition rely less on an allocentric spatial representation.

Alternatively, a list length of two items might have reduced difficulty to the extent, it could be argued, as to make it possible for patient Jon and other temporal lobe patients to store both item locations in an egocentric spatial framework with the need to mentally rotate them both. Such egocentric representations would be more affording in terms of capacity than a combined (map-like) representation of several object locations and thus vulnerable with increasing memory load and delay. It has indeed been demonstrated before that Jon's performance in a task that can be solved using an egocentric strategy decreased for high list lengths (King et al., 2002). The pattern of Jon's performance on

[1] This does not imply that propositional encoding of the kind "under" and "next to" necessarily rely on verbal encoding, but is suggested as an additional *phonological* encoding strategy.

single items at list length 4 in the same view condition, see Fig. 5.4, would be further in line with this argument. Performance dropped systematically with increasing numbers of items between study and test. To further test this hypothesis, the robustness over time of Jon's seemingly intact representation in the rotated view could be investigated.

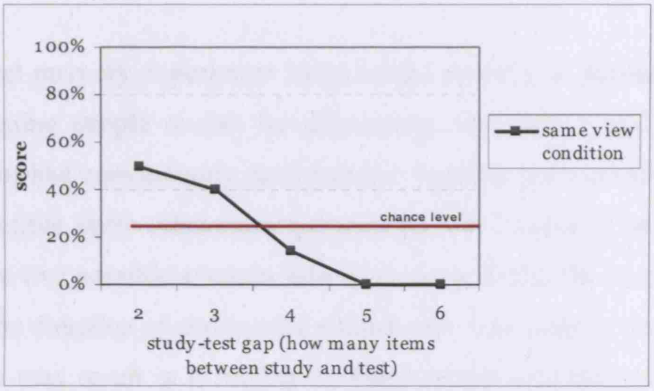


Figure 5.4 Jon's performance in the same view condition of experiment 1, over study-test gap (how many other items occur - as study or test items - between study and test of an item): Performance decreases with number of items between presentation and test.

A final argument concerns the difference between mentally rotating (updating) an array in respect to one's viewpoint as opposed to mentally rotating (updating) one's viewpoint around the array. Inagaki et al. (2002) have shown that elderly people perform worse than younger in the former but not the latter form of mental orientation updating process. This leads us to think that one but not the other, namely mentally moving one's viewpoint around an array but not rotating the array, might be hippocampal-dependent. It would seem that the virtual reality setting promoted the hippocampal-dependent type of mental updating while the lego-model, due to a decreased feeling of immersion in the miniature environment, might promote another kind. This is further compatible with Jon's and other bilateral hippocampal (Holdstock et al., 2000) and unilateral temporal lobectomy patients' (Abrahams et al., 1997) intact performance on tasks of mental rotation like the Little Man test (Ratcliff, 1979).

In conclusion, it appears that intact hippocampal functioning and the resulting availability of both ego- and allocentric representations exhibits a clear advantage in dealing with the same view task of the lego experiment, whereas, by contrast, the affordance of the rotated view condition is not high enough as to exhaust an egocentric encoding strategy.

The topographical memory experiment using a lego model was developed as a test for sensitively screening people at risk for developing Alzheimer's and a virtual reality version of the test had convincingly demonstrated hippocampal sensitivity in an elderly patient with possible early Alzheimer's dementia, see Chapter 4 and Burgess et al. (2005). There are two possible avenues how to proceed: Either the virtual version could be modified in the direction of making the shifted view task easier – as making the same view task harder may result in it relying on hippocampal function – e.g. by equipping the virtual landscape with additional landmark features to facilitate reorientation after viewpoint shift, or by reducing the angle between presentation and test. Alternatively, the lego experiment could be modified in terms of increasing the distance between target and foil locations for the same view task, and increasing the list lengths so as to undermine short-term egocentric or verbal encoding for the rotated view condition.

Over all, the manipulations and adaptations of the topographical memory experiment under development have led us to understand further how its virtual reality predecessor works in terms of tapping egocentric versus allocentric spatial representations. This is why it seems favourable to pursue its progress for use in the screening of people with a higher risk to develop Alzheimer's disease, because we can argue convincingly on what neural basis it works (the distinction between a condition that relies on allocentric spatial representations and one that can be solved on the basis of egocentric spatial representations) and why (because allocentric spatial representations rely on hippocampal functioning), unlike other neuropsychological tests that have been found to distinguish between people who later develop dementia and people who remain well (Fowler et al., 2002; Swainson et al., 2001).

Chapter 6) Discussion of Part I

The hippocampal role in successful allocentric wayfinding in normal human subjects has been strongly confirmed by recent neuroimaging experiments (e.g. Ghaem et al., 1997; Hartley, et al., 2003; Maguire, et al. 1998a; Morris & Mayes, 2004}. However, clinical evidence of a purely allocentric spatial impairment in connection with hippocampal pathology has remained largely undemonstrated (but see Maguire et al., 1996a; Morris et al., 1999). We have argued that a lack of sensitive testing of purely allocentric spatial representations was accountable for this, a gap that the experiments presented in the first part of this thesis tried to fill.

One difficulty with which previous attempts struggled (Holdstock et al., 2000) was the need to introduce a new viewpoint at testing of a spatial representation to provoke use of representations relative to the environment and independent of the viewer's standpoint, without allowing movement-related updating of egocentric spatial representations. Virtual reality paradigms in which instantaneous teleportation is possible offer such qualities. Also, miniature environments that can be moved as a whole in respect to the viewer's vantage point were hypothesised to lead to the same effect.

A previously developed topographical memory experiment using virtual reality (King et al., 2002) was successfully adapted in Chapter 3 to contain two conditions of comparable difficulty for healthy young participants. One condition relied on an allocentric spatial representation, while the other condition could be solved using an egocentric spatial representation that did not rely on the hippocampus. Difficulty was matched probing memory for object locations using foil locations close to the target location in the same view condition and more widely spread foil locations in the shifted view condition. It was shown that hippocampal damage selectively disrupted allocentric memory in a young developmental amnesic, patient Jon (see Chapter 3 and King et al., 2004).

Topographical Disorientation

The above paradigm was used to assess a patient, C.F., who presented with topographical disorientation (see Chapter 4 and Burgess et al., 2005). We found the same dissociation between intact egocentric and impaired allocentric topographical memory as in patient Jon. We hypothesised that the patient's deficit might be caused by hippocampal pathology which would be consistent with her diagnosis of probable early Alzheimer's disease, and further supported by her impaired performance in a virtual reality wayfinding task for which Maguire et al.(1998a) had demonstrated an association between hippocampal activation and navigation accuracy. The patient showed relatively preserved performance on various other neuropsychological tests. Her deficit in allocentric memory most accurately captures her 'topographical disorientation'. This demonstrates the utility of considering allocentric spatial memory as an additional cognitive process category underlying topographical orientation (next to the ones suggested by Aguirre & D'Esposito 1999).

The selective allocentric spatial memory impairment contrasted with the patient's preserved verbal recall. This speaks against evidence reported elsewhere that verbal memory decline might most sensitively mark the onset of Alzheimer's disease (Fox et al., 1998; Hodges & Patterson, 1995). However, it fits with reports that a significant difference in non-verbal paired associate learning most sensitively distinguishes between patients with questionable dementia and normal healthy controls (Fowler et al., 2002; Swainson et al., 2001). An alternative explanation could be that the premorbid verbal capacities of patient C.F., who had been a teacher, were higher than normal, concealing any mild verbal memory impairment. In comparison, patient Jon, with much more severe and definitely bilateral hippocampal damage shows allocentric spatial memory impairment on the one hand and impaired verbal recall memory on the other hand (Vargha-Khadem et al., 1997). It would be interesting to pursue the further development of patient C.F. It could be that a selective spatial memory deficit became confirmed structurally with selective right hippocampal dysfunction, corroborating the hypothesis of lateralised hippocampal function (verbal on the left and spatial on the right), proposed by the Cognitive Map theory (O'Keefe & Nadel, 1978).

Difference between egocentric and allocentric memory performance in normal elderly participants

Another finding of Chapter 4 concerned a significant difficulty difference between the two testing conditions (egocentric versus allocentric memory) for a group of healthy elderly participants, when the test had been difficulty-matched in the younger population using closer foils for the same view condition. Such a performance decrease in allocentric as opposed to egocentric spatial memory in healthy elderly subjects as compared to the young has also been reported by other authors (Driscoll et al., 2005; Monacelli et al., 2003). However, rather than following this difference, we attempted to equalise performance across conditions for elder participants so as to avoid problems of interpretation when using the test to assess hippocampal pathology. Also, the clinical practicability of the use of virtual reality with some elderly subjects was of concern, notwithstanding that the immediate viewpoint change in the allocentric condition is only possible in virtual reality.

As an alternative to virtual reality, we thought of testing topographical memory within a miniature environment that can be rotated intact. If the object locations to be tested are removed from view, the local landmarks can be changed without the viewer being able to use movement-related updating of an egocentric representation of the object locations. This test was implemented in Chapter 5 keeping the manipulation of foil-spacing used in the virtual reality test, namely spreading the foil locations evenly in the shifted view condition as compared to close foils in the same view condition. Results from Chapter 5 (experiment 2) revealed a seemingly satisfactory difficulty-match between the same and rotated view condition in a group of healthy elderly participants. However, when patient Jon and a group of elderly patients with hippocampal pathology were tested, they both showed a performance increase from same view to rotated view conditions. Thus, on the one hand a test of object location from a different point of view had become feasible for hippocampal patients. On the other hand a test of object location from the same point of view yielded worse performance than the test from a different point of view in hippocampal patients.

In an attempt to explain this outcome, rather than doubting the hippocampal role in allocentric spatial memory, we would like to make use of previous findings in the context of the topographical memory experiment (see Chapter 3 & 4, King et al., 2002; 2004) to explain these results.

The difference between imagining moving one's viewpoint and mental rotation

Firstly, as was argued in Chapter 3, there are circumstances under which the same view condition, which could normally be solved using an egocentric strategy, would be supported by an allocentric representation. These involve storage capacity limitations, as it could be that egocentric representations for each object location have to be stored separately whereas allocentric representations can be merged into a single, map-like representation (Burgess et al., 2002). Another situation promoting the use of an allocentric representation involves long delays between study and test, as egocentric representations may be more transient – occurring in working memory - compared to allocentric representations which may occur in long-term memory. Evidence for such capacity limitations of egocentric representations in patient Jon performing the same view task is twofold: On the one hand it has been shown by King et al. (2002) that Jon's performance in the same-view task became successively more impaired for list lengths greater than three. On the other hand, we showed in Chapter 5 that his performance for single items in the same view condition depended on the number of intervening items tested, and dropped to chance with higher item-gaps between study and test. Further in line with this hypothesis is the finding of Holdstock et al. (2000) that Y.R., a patient with selective bilateral hippocampal pathology, was significantly impaired in a spatial updating experiment for a 60s delay compared to a 5 s delay.

Secondly, these findings might tell us something about the role of the hippocampus in the spatial updating involved when physically or mentally moving around to obtain a new vantage point compared to moving the array or imagining moving the array (see also Burgess et al., 2004; Wang & Simons, 1999; Wraga et al., 2000). Holdstock et al. (2000) showed that patient Y.R. was impaired on the former spatial updating task whereas her performance is intact on the latter tasks of mental rotation like the Little

Man test (Ratcliff, 1979). Further, Inagaki et al. (2002) showed that elderly people perform worse than younger in the former but not the latter kind of a mental updating process. Together with the finding that elder participants also show decreased performance in allocentric spatial memory tasks like e.g. the Morris water maze task (Driscoll et al., 2005; Monacelli et al., 2003), this leads us to think that moving one's own viewpoint around an array is hippocampal-dependent whereas rotating the array is not. The topographical memory experiment using virtual reality appears to require imagined movement of one's viewpoint around the array rather than mental rotation of the array. By contrast, the experiment using a lego town appears to have enabled the use of mental rotation. It could be that this difference is correlated with subjects' prior experience of movement of viewpoint through the virtual environment on the one hand and of seeing the rotation of the lego town on the other. One consequence of this interpretation is that performance on the lego town rotation condition should reduce at larger list lengths, compared to the virtual reality test, since mental rotation of the array should be less efficient than mental movement of viewpoint (Wraga et al., 2000).

In summary, the experiments conducted in Part I suggest that remembering object locations following an abruptly introduced new viewpoint on a spatial scene requires an allocentric spatial representation that is dependent on the hippocampus. This task may be solved by remembering where the objects are relative to landmarks in the environment, or by mental manipulation of viewpoint to imagine what the stored scene would look like from the new viewpoint. By contrast, mental rotation of single objects, or even of small arrays, might be hippocampal-independent. In normal elderly subjects the capacity to form this allocentric spatial representation is decreased in comparison to a younger population. However, there was still a significant difference in performance on this task between healthy elderly subjects and a patient with probable Alzheimer's disease. This corroborates the usefulness of a topographical memory test tapping allocentric spatial representations in sensitively screening early signs of hippocampal pathology known to occur in Alzheimer's disease (Braak & Braak, 1991).

Chapter 7) Introduction to Part II Hippocampal involvement in episodic memory

Overview over Introduction to Part II

In the first part we saw that hippocampal function in human subserves allocentric spatial memory. This role of the hippocampus is shared between humans and animals (e.g. Ekström et al., 2003; Ghaem et al., 1997; Maguire et al., 1998a; Morris et al., 1999c; Morris et al., 1982; O'Keefe & Nadel, 1978). The second part of this thesis is about what the reader probably expected in a thesis "about memory". In everyday language, remembering mostly refers to "episodic memory" (Tulving, 1983), for example: "Do you remember that day we had that discussion about Nanobots, over lunch, with Tom and John in the ICH cafeteria. It was Friday and we had Fish and Chips. With Peas. The Fish was nice and crunchy but the peas were too salty." This kind of episodic memory is specific to humans (Tulving, 2001), however there are recent reports of very similar kinds of episodic-like memories in other species (Clayton & Dickinson, 1998). As was mentioned in the General Introduction (Chapter 1), the term 'episodic memory', referring to memory for personally experienced events, was carved out in differentiation to 'semantic memory', memory for factual information (Tulving, 1972; 1983). Episodic memory includes information about what happened and a specific spatial and temporal context. The "prototypical unit of an episodic memory is an event" as suggested by Tulving (1983, p.223), and the different elements of an event are thought to be strongly tied together to provide a single encapsulated unit, allowing "re-experience" of all aspects of the event simultaneously at retrieval (Tulving, 1972; 1983; 2002).

Chapter 8 looks at this "binding" in episodic memory. Chapters 9 and 10 present functional neuroimaging experiments that each deal with a different aspect of real-world episodic memories. Chapter 9 investigates the effects of the personal significance of stimuli on the neural systems involved in encoding and retrieval, using photographs of participants' personal acquaintances as compared to publicly known (famous) people or unknown people in a recognition paradigm. Chapter 10 explores the effect of the

modality of an event's context (spatial or olfactory) on the neural systems involved in retrieving that event's content via a contextual cue.

This introduction starts by discussing the theoretical positions and experimental evidence related to how events are bound together in episodic memory. Subsequently the neural bases of episodic memory are elucidated, with a particular emphasis on the role of the hippocampus. Additionally, the respective role of other areas of the brain activated in fMRI studies on episodic memory retrieval is discussed. Further, I talk about the difference between episodic memory as traditionally tested in laboratory experiments and retrieved autobiographical episodes, focusing mainly on the aspects of personal relevance, memory age, emotionality and multimodality. The role of the hippocampus in respect to these attributes will be debated. A separate paragraph is further devoted to the discussion of the correlation between memory age and hippocampal activation and of the role of the hippocampus in emotional memories. The last paragraph introduces olfactory memory in order to prepare the studies presented in Chapter 8 and 10 in which olfactory context was used to explore multimodal episodic memory.

The binding structure of episodic memory – "Part or parcel"?

Chapter 8 examines the structure of episodic memory, asking whether or not events and their context do form the units of episodic memory (Trinkler et al., in press). Taken at face value this would imply that episodic memory is holistic in that whenever an event is recalled, *all* of its elements are remembered together. Alternatively, memory for different elements of an event might be remembered or forgotten *independently*. In Chapter 8, 'holistic' is operationalised in terms of the size of the correlation between retrieval performance on different aspects of the same event. A fully holistic view would predict maximal correlation between retrieving an event via one cue and retrieving the same event via another cue. On the other hand, a fully fragmented view or 'independent model' of memory for the many pair-wise associations comprising an event would predict no such correlation. Support from previous research can be found for both views

(holistic or fragmentary) of episodic memory processing. The holistic view seems central to Tulving and colleagues' theoretical stand point, who see episodic remembering as "the kind of awareness that characterises 'mental re-living' of happenings from one's personal past..." (Düzel et al., 1997 p.5973). The full retrieval of the manifold aspects in episodic memory distinguish it from semantic memory.

O'Keefe and Nadel (1978) further seem to take a holistic viewpoint of equal and symmetric cue processing. In the Cognitive Map theory, the locale system refers to "memory for items within a spatio-temporal context", thus to episodic memory. Specifically, the locale system is argued to provide multiple channels of access such that any relationship in the map can be retrieved by activating any other portion of the map, whether or not these relationships were noticed at the time of input (see O'Keefe & Nadel, 1978, p.384). A similar idea seems to be represented by Fisher and Chandler who remark that the episodic memory system "treats information in a close temporal-spatial proximity as an event that is represented in an *isolated* trace. Later activation of that trace produces recollection of that specific event" (Fisher & Chandler, 1991, p.722). This theory is based on the observed independence between the recall of different event sets. Eichenbaum and Cohen's theory of relational memory (Eichenbaum & Cohen, 1988; 2001) maintains the idea of flexibility from the cognitive map. It is thought that information should be retrievable via a variety of cues. However, the theory puts more stress on pair-wise associations, and so a holistic representation is not necessarily implied. A study by Brewer and Dupree (1983) suggests further that for at least some types of events, recall appears to be all or none. In their experiments participants were shown movies in which actors performed goal directed actions. In some cases there was a causal link between elements in the event and in others the link was solely temporal. Recall of the causally related events tended to be all or none, while the recall of the non-causally related events tended to be less well correlated. Also visual elements of an event, consisting of the aspects object, colour and location on the display, were shown to be stored as holistic fragments (Jones, 1976). Jones (1976) additionally suggested that the fragments were equally effective as retrieval cues and used symmetrically, retrieval of element A by element B was equally good as retrieval of element B by element A.

This symmetrical use of cues was proposed before by Asch and Ebenholz (1962). In order to test whether these retrieval characteristics of episodic memory would hold for real-world episodic memories which contain much richer context-elements, Wagenaar (1986) studied (his own) everyday memories over a period of four years. He attempted to recall different autobiographical events recorded over that time, by probing himself with different elements of each event (who, what, when and where). In contrast to Jones (1976) he found marked differences in the usefulness between retrieval cues and asymmetry in their processing: He found 'what' to be the best cue, while 'where' was slightly better than 'who'. The observation that not all elements of an event will serve as equally effective retrieval cues was also stressed by Marr (1971) in his description of simple representations, and further in the Headed Records Model of memory (Morton et al., 1985; Morton & Bekerian, 1986). Wagenaar interprets the differences between his study and Jones' in terms of differences in cue specificity. In Jones' study, within each list of nine events, each cue was specific to only one event, whereas Wagenaar's cues varied in specificity. More specific cues might be more efficient in prompting retrieval, and many less-specific cues might, in Jones' terms, be contained in very many fragments.

The approach taken in Chapter 8 to investigate this matter further attempts to bridge between the laboratory experiment that lacks a certain amount of external validity and the real-world-experiment of Wagenaar (1986) that in its turn suffers from lack of controllability over memory material. To that end, the binding of various elements of context of an event with the event's content in episodic memory was investigated using a computer based virtual reality paradigm involving pseudo-realistic, simulated events. The experimental setting involved participants following a trail through a virtual reality town and meeting virtual characters in different places who present them with objects. Later, the retrieval of which object went in which place with which person is tested by forced choice recognition.

The experiment presented in Chapter 8, and previous versions of the same paradigm, also served to investigate the neural bases and in particular hippocampal-dependence of

context-dependent memory as compared to pure object-recognition. This important functional distinction between a general sense that the stimulus has been encountered before ('familiarity-based recognition') and specific retrieval of an event and its context ('episodic recollection') has been suggested in many psychological studies (e.g. Jacoby et al., 1993; Mandler, 1980; 1991; see Yonelinas, 2002 for a review) and more recently has been proposed to be supported by two distinct neural systems, which we consider next:

"The extended hippocampal system" ; recognition versus recollection in two neural circuits

Based on lesion studies in animals Aggleton and Brown (1999) suggested that a diencephalo-hippocampal circuit supports episodic recollection, while a distinct parallel thalamo-perirhinal system supports familiarity-based recognition (see Fig. 7.1). There is evidence showing that the perirhinal cortex is important for knowledge about objects (Suzuki, 1996), whether they are familiar and whether they have been associated with other discrete visual inputs. It is assumed that this route normally provides item-related information to the hippocampus that may be retained in episodic memory. The to-be-remembered item is then set within its episode or context, and for this association to be possible the hippocampus must receive spatial/ contextual information. In the primate brain the most plausible route for this is via the parahippocampal cortex which permits item-place representations to be formed (Aggleton & Brown 1999).

Both the perirhinal cortex and the hippocampal formation connected to it entertain independent links with other association cortical areas. Further, each have independent roles in the encoding of episodic information and familiarity-based recognition. Whereas the perirhinal cortex makes connections with the medial dorsal thalamic nucleus, the hippocampus is linked to the anterior thalamic nuclei. The entorhinal cortex is thought to have aspects of both systems.

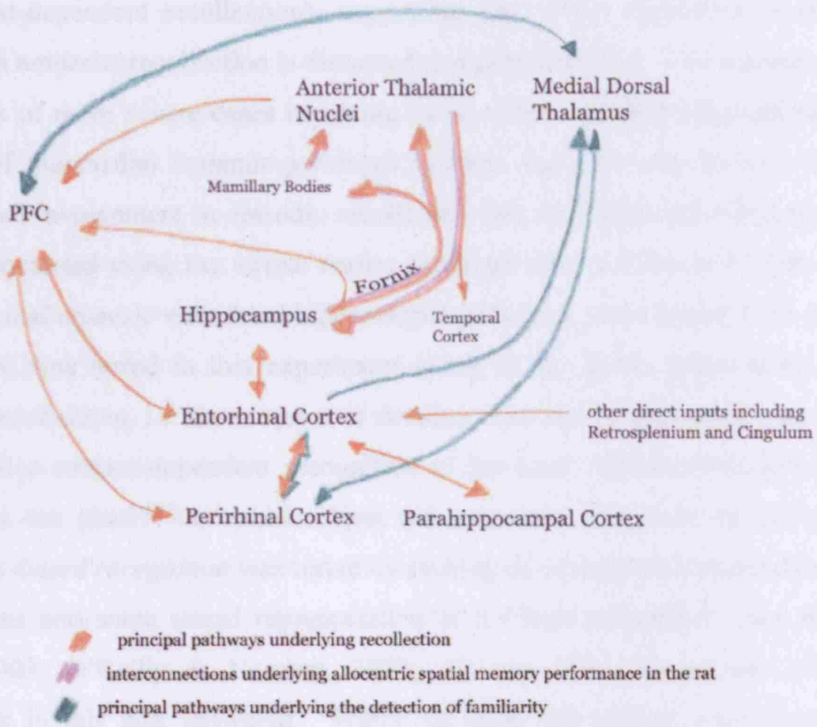


Figure 7.1 Illustration of the distinct pathways underlying recollection versus familiarity-based recognition, modified from Aggleton and Brown (1999).

The "extended hippocampal system" permits information to be set in its spatial and temporal context, aiding subsequent retrieval. It includes hippocampal efferents to the medial diencephalon which are regarded as vital for normal hippocampal functioning. The anterior thalamic nuclei receive direct hippocampal projections via the fornix and indirect hippocampal projections via the mammillary bodies and the mammillothalamic tract. Other thalamic nuclei that may contribute to this system are the rostral midline nuclei and the lateral dorsal nucleus. The system beyond the anterior thalamic nuclei becomes more diffuse, but one component, which mainly uses the cingulum bundle, projects back from the anterior thalamic nuclei to the hippocampus and to adjacent temporal cortical regions. Other important outputs are to the cingulate and prefrontal cortices.

A recent neuropsychological review (Rugg & Yonelinas, 2003) concluded that clinical data in humans are in support of the dual-process model (familiarity-based recognition and context-dependent recollection), suggesting that, while familiarity is commonly impaired in amnesia, recollection is disrupted to a greater degree. This is congruent with lesion sites of more severe cases involving more of the extended hippocampal system and less of the medial thalamic-perirhinal system. Aggleton and Brown's notion of hippocampal involvement in episodic recollection but not familiarity-based recognition was directly tested using the virtual reality paradigm used in Chapter 8. Patient Jon, a developmental amnesic with focal hippocampal pathology, see Chapter 3 for a detailed description) was tested in this experiment (King et al., 2004; Spiers et al., 2001a). Episodic *recollection*, i.e. the retrieval of detailed contextual information, was tested by forced choice context-dependent recognition of the kind "which object (of two) was received in this place?" or "which object (of two) were you given by this person?". *Familiarity-based recognition* was tested by probing the strength of the match between a test stimulus and some stored representation of it ('item recognition', see Bogacz & Brown, 2003; O'Reilly & Norman, 2002; Tulving, 2001; Yonelinas, 2002). The participants in this task answered, "Which of these two objects were you given?". Familiarity-based recognition would be sufficient to decide which of two items had been encountered before but would not be sufficient to decide which of two familiar items had been received in a particular context. (Note that episodic recollection on the other hand allows one to solve either task.)

The earlier version of this virtual reality paradigm (Spiers et al., 2001a) contained only two spatial contexts and two virtual characters who presented participants with various objects. When patient Jon was tested, he showed impaired contextual recollection on the one hand and relatively spared familiarity-based recognition on the other hand. However, normal healthy participants also performed better at the familiarity-based recognition task than at contextual recollection, which caused a problem interpreting the findings. The object-recognition task was easier than the context-dependent tasks as judged by the average scores of the healthy control participants. Thus the possibility remained that a non-linear effect of difficulty might have accounted for the steeper

declining performance of Jon compared to controls between the familiarity-based and the context-dependent recognition task. Moreover, this could have been related directly to the limited number of virtual people and places creating the virtual events causing a high degree of interference. King et al. (2004) using the exact paradigm presented in Chapter 8 attempted to match performance between the tasks, including 20 events, involving distinct characters and places. Their study successfully replicated Spiers et al.'s (2001a) major outcome, finding patient Jon impaired in context-dependent memory but performing normally on object-familiarity. This adds evidence that the hippocampus is involved in context-dependent recollection but that extra-hippocampal structures support familiarity-based recognition, as postulated by Aggleton and Brown (1999).

We are further interested in the other structures that, together with the hippocampus, support context-dependent episodic recollection. These have been revealed mainly by functional neuroimaging studies. They will be introduced shortly. However, we first consider neuroimaging of the hippocampus itself in episodic memory:

Hippocampal activation in neuroimaging studies of episodic memory

While patient studies have long implicated the medial temporal lobes in episodic memory (e.g. Baddeley et al., 2001; Fortin et al., 2002; Kinsbourne & Wood, 1975; Mayes et al., 1985, 2001; Vargha-Khadem et al., 1997; Yonelinas et al., 2002), many early neuroimaging studies on episodic memory have failed to show hippocampal activation during episodic memory processes (e.g. Shallice et al., 1994; Tulving et al., 1994b). On the one hand it could be argued that traditional stimuli used as memory material (wordlists) lacked naturalistic context and that it did not tap hippocampal function. This argument forms the basis of experiments with naturalistic context-dependent recollection paradigms, such as the virtual reality paradigm used by Spiers et al.(2001a) and King et al. (2004) and see Chapters 8 and 10.

On the other hand, early it was also hypothesised that the hippocampus is continuously and obligatorily engaged in *encoding* new information (Fletcher et al., 1997, Moscovitch, 1995). If the hippocampal formation encodes new information

automatically and involuntarily, contrasts between studied and unstudied items in recognition memory tests would fail to yield differential activation as retrieval-related activity associated with old items and encoding-related activity elicited by new items would cancel. The hippocampal role in "spotting the new" has been directly investigated by Strange et al. (1999). Using fMRI, they demonstrated a left anterior hippocampal response to both perceptual (change of font size) and exemplar novelty. Moreover, these responses were found to adapt with stimulus familiarity. By contrast, bilateral posterior hippocampal responses were shown with increasing exemplar familiarity, expressed only for aspects of stimuli relevant to learning. The authors concluded that a function of the anterior hippocampus is to register mismatches between expectation and actual experience. Congruent with this, anterior hippocampal activation has recently been found in a mere stimulus detection task involving new visual-olfactory stimulus-combinations (Gottfried & Dolan, 2003).

The retrieval network of episodic memory outside the hippocampus

In neuroimaging experiments on episodic memory, a wide-spread network of areas has been found beyond the medial temporal lobes, associated with episodic memory retrieval (see Maguire, 2001a for a review, and further Burgess et al., 2001b; and King et al., 2005), including the retrosplenial cortex, temporo-parietal junction, medial frontal cortex, temporal pole and cerebellum. The following sub-sections explore how these various structures might contribute to episodic memory retrieval.

The temporal lobe: Interplay between autobiographical and semantic memory

In patients with semantic dementia, with pathology primarily occurring in the (left) lateral temporal lobe, semantic information including public events knowledge is succeedingly diminished, while patients have relatively preserved recall of autobiographical events, at least at initial stages of the disease (Graham & Hodges, 1997; Hodges & McCarthy, 1995). According to Damasio, the temporal poles encode the spatiotemporal uniqueness of specific events and integrate information from hippocampal structures with information from posterior association regions (Damasio,

1989b). In line with this hypothesis, Maguire et al. (2000) found effective connectivity between the temporal pole and the parahippocampal cortex, and between the parahippocampal cortex and the hippocampus, in autobiographical event retrieval. Graham et al. (2003), reported right anterior temporal lobe activation for autobiographical recall and for retrieval of information about famous people or events compared to retrieval of general semantic facts. We thus see some differentiation of the lateral temporal lobe. The temporal pole appears to be associated with the retrieval of information that is more autobiographical or event-related. On the other hand, effective connectivity between the middle temporal gyrus and temporal pole was significant during retrieval of general knowledge and public events (Maguire et al. 2000), thus more semantic memory. Thus, the picture appears to be more complicated than the idea of a homogenous shift from episodic to semantic memory medially to laterally in the temporal lobe. This view is also put forward by Kapur & Kopelman (2001).

An interesting further investigation of the interaction between knowledge representations and episodic memory retrieval presents research into autobiographical significance of semantic knowledge as a factor in determining patterns of semantic loss caused by brain damage (Snowden et al., 1999; Westmacott & Moscovitch, 2003; Westmacott et al., 2004). Westmacott et al. (2004) presented control participants and groups of different memory patients with famous names that had been rated on various attributes, and non-famous distractor names. The famous names ratings had been done by control participants in a norming study and included a rating of autobiographical significance. Participants in the main experiment indicated whether they recognised the name. Semantic dementia patients were found to be more likely to recognise, identify and remember famous names rated high in autobiographical significance and showed an advantage in reading accuracy and recognition for those names they could identify and recognise, similar to controls. Westmacott et al. (2004) speculate that this performance advantage for autobiographically significant knowledge reflects the relative sparing of autobiographical memory and medial temporal lobe regions in semantic dementia. By contrast, patients with Alzheimer's disease and patients with medial temporal lobe amnesia typically fail to show the effect of autobiographical significance on tests of

semantic memory because their autobiographical memory is deficient and has very little to contribute to their performance. Insofar as some few autobiographical memories are spared, however, these patients' performance on tests of episodic and semantic tests continue to be influenced by them (Westmacott & Moscovitch, 2003). Thus, the findings of Westmacott et al. (2004) suggest that autobiographical memory also contributes to remote semantic memory by helping to "preserve the detailed richness of personal experience that embellish conceptual representations or are integrated with them"(p.42).

Conway (2001) however argues that there is an important distinction between autobiographical event memory and autobiographical knowledge and that the latter can be accessed independently of episodic memories and is independent of hippocampal functioning. It is hypothesised that when this occurs, recollective experience is absent. Instead, access is accompanied by feelings of knowing. Importantly, Conway (2001) further argues that autobiographical memories are effortfully constructed using different types of autobiographical knowledge (life events, general events, sensory-perceptual episodic memories) in a nested process of retrieval that requires time (Conway et al., 1999, claim beyond 5s). In line with this, in patient Jon activation of the remaining viable hippocampal tissue was shown when recollection included vivid re-experience of an autobiographical episode, but not for merely "knowing that an event occurred" (Maguire et al., 2001b). Moreover, a recent functional imaging study with a patient with adult-acquired anoxic hippocampal pathology, V.C., revealed no hippocampal activation at retrieval of personal events (Maguire et al., 2005). V.C. presents with a profound memory loss including autobiographical and public event memories extending far back. He is able to report only a few highly stereotypical memories. The findings suggest that indeed the detailed richness of event memories is hippocampal-dependent, but that, on the other hand, there are aspects of autobiographical knowledge that are stored outside the hippocampus.

Prefrontal cortex

Early neuroimaging studies on episodic memory (e.g. Shallice et al., 1994; Tulving et al., 1994b) that failed to find hippocampal activation, by contrast revealed an apparent strong involvement of the frontal cortices in memory. This caused developing interest in the role of prefrontal cortex in memory (see Wheeler et al., 1997, and Simons & Spiers, 2003, for reviews).

There are large cortico-cortical direct reciprocal connections between the prefrontal cortex and the medial temporal lobe. More specifically, the orbitofrontal and dorsolateral cortices have strong reciprocal connections with the perirhinal and entorhinal cortices (Rempel-Clower & Barbas, 2000). Both are further strongly connected to the caudal posterior cingulate cortex and amygdala (see Maddock et al., 2001, for an overview).

Despite a strong involvement of prefrontal cortex in episodic memory retrieval and important reciprocal connections between the prefrontal cortex and the temporal lobes, lesions of the prefrontal cortex are known to have only a limited effect on many tests of episodic memory, "unless highly elaborate encoding or retrieval strategies are required" (Fletcher et al., 1997, p. 213). Patients with frontal lobe dysfunction are specifically impaired when there is significant interference between stimuli to be recalled (Incisa della Rocchetta & Milner, 1993). In line with this, widespread lateral and anterior prefrontal activation was found in the earlier version of the virtual reality paradigm described above (Burgess et al., 2001b), in which the high repetition of the contextual elements 'person' and 'place' caused high interference. Further evidence for this has been shown in a recent replication experiment (King et al., in press). Interference was markedly reduced when distinct people and places defined each event uniquely, and the strong prefrontal activation diminished.

Another memory disorder associated with frontal lobe damage, particularly in the ventromedial prefrontal cortex, is confabulation (Burgess & Shallice, 1996; Moscovitch, 1989). It might be the result of impairment to memory control processes, retrieval cue specification on the one hand and monitoring and verification of retrieved information

on the other hand (Simons & Spiers, 2003). The two processes are supposedly supported by the ventrolateral and dorsolateral prefrontal cortices respectively. Note that this is not congruent with the typically reported site of the prefrontal impairment associated with confabulation. See further below for a continuing discussion of the function of more ventromedial areas.

The ventro*lateral* region of the prefrontal cortex (BA44,45,47) is thought to be involved in the elaborative *encoding* of information into episodic memory (Henson et al., 1999a; Wagner et al., 1998), as well as in the specification of *retrieval* cues (Dobbins et al., 2002) and the maintenance of retrieved information (cf. working memory, D'Esposito et al., 1999; Wagner et al., 2001). The region can be further subdivided into anterior and posterior portions, which are suggested to subserve semantic processing and lexical or phonological control processes respectively (Dobbins et al., 2002; Poldrack et al., 1999; see Simons & Spiers, 2003).

Dorsolateral prefrontal cortex (BA46/9) is considered to be involved in the organisation of material before encoding (Fletcher et al., 1998). As, for example Tulving et al. (1994b) have proposed, any verbal mediation, associated with left prefrontal activation, will facilitate memory. When volunteers are intentionally trying to remember a list of words, they are likely to adopt such facilitatory encoding strategies. However, left prefrontal activations are associated with word-generation tasks, even if subjects do not try to memorise. Therefore, it seems that left prefrontal cortex activation at encoding is more likely to be related to the application of *automatic* encoding operations (Fletcher et al., 1997). Furthermore, dorsolateral prefrontal cortex is thought to be involved in the evaluation of representations that have been retrieved from long-term memory and are maintained by ventrolateral frontal cortex (Dobbins et al., 2002; Petrides et al., 1993; Rugg et al., 1999; see Simons & Spiers, 2003).

The roles of the lateral prefrontal cortex in memory encoding are summarised and integrated in Simon and Spiers' (2003) "unifying framework". It is proposed that to be encoded information is primarily processed by uni-modal and poly-modal cortical areas

before being transmitted to the medial temporal lobe. At that stage, the interaction with prefrontal cortex provides top-down control of the encoding processes, elaborating the representations in the medial temporal lobe on the basis of current goals and task demands, ensuring that the representations are sufficiently non-overlapping (Henson et al., 1999a; Wagner et al., 1998; in Simons & Spiers, 2003). Thus, disconnection of ventrolateral prefrontal cortex and the medial temporal lobe can be expected to have a greater impact when retrieval cues are poorly defined. The elaborated retrieval cue is used to "interrogate" the medial temporal lobe (Simons & Spiers, 2003), strategically searching stored representations and matching the cue with stored information, possibly through pattern completion (McClelland et al., 1995). When one or more candidate memories have been identified, their representation will be maintained in working memory by ventrolateral prefrontal cortex while monitoring operations, supported by dorsolateral prefrontal cortex, are engaged to compare the retrieved information with the specified retrieval criteria. This allows the disambiguation of competing memories (Henson et al., 1999b; Rugg et al., 1999; Schacter et al., 1997; see Simons & Spiers, 2003). This most recent synthesis of prefrontal processing incorporates and updates earlier models like Lepage et al.'s (2000) "retrieval mode" (REMO) function of prefrontal cortex (see also Tulving, 1983; and Nyberg et al., 1995) and its forerunner, the HERA model (Tulving et al., 1994a).

This framework does however not include the rostromedial prefrontal cortex (BA10), and adjacent orbitofrontal area BA11. Rostromedial prefrontal cortex (BA10) has been reported to show "task-induced de-activation" (Shulman et al., 1997) and the common explanation attributes its function to ongoing internal processes (McKiernan et al., 2003) or the "ultimate state of inspection of the self" (Wicker et al., 2003 p.229). If that were the case that would mean that activation was task-unrelated and stimulus-independent. Some authors however hypothesise that the medial prefrontal cortex monitors attention towards the external input (Gilbert et al., 2005a). Gilbert et al. (2005a) showed rostromedial prefrontal cortex involvement during directing attention towards the external environment as operationalised in the contrast between stimulus-oriented (visual stimulus processing) and stimulus independent (silent adding) mental activity.

The authors further controlled for the argument that subjects could have been simply daydreaming more, showing that the area correlated positively with faster reaction times (Gilbert et al., 2005b). Thus, the rostral medial prefrontal cortex seems to be involved in biasing attentional balance between sensory input and internally generated thought.

However, returning to the idea of 'self'-relevant processing, the medial surface, in particular medial orbitofrontal cortex (BA 11), has been further attributed a role in retrieval of information in relation to the 'self' (Levine et al., 1998; Maguire et al., 2001b; see Maguire, 2001a for an overview). For example, Cabeza et al. (2004), in a study on autobiographical memory (described further on page 110), found lesser deactivation in medial prefrontal cortex. It was attributed to retrieving stimuli attributed to the 'self' compared to stimuli attributed to others.

In a PET-experiment by Craik and colleagues on the "neural correlates of the self" (Craik et al., 1999), subjects were asked to judge trait adjectives according to how well the words described them ('self'), how well they described someone else ('other') how socially desirable the traits were ('general') and how many syllables the trait word contained ('syllable'). The behavioural results were consistent with the self-reference effect (Rogers et al., 1977) that states that a person remembers a word (e.g. "stubborn") better after answering self-referential question ("Does this adjective describe you?") than after answering a general semantic question (e.g. "does stubborn mean the same as obstinate?") (Craik et al., 1999). Note however that when the other person is well known, subsequent memory levels have been found to be almost as high as those associated with self judgment (Bower & Gilligan, 1979; Keenan & Baillet, 1980). Congruently, Craik et al. (1999) found that subjects remembered self and other adjectives equally well and better than the ones from the general and syllable conditions. Imaging results revealed an effect of self-related encoding (when 'self' was contrasted to 'other', 'general' and 'syllable' combined) in left frontal regions, including left and right medial frontal cortex (BA10/9) and inferior frontal gyrus (BA45). 'Self' versus 'general' revealed activation in the right anterior cingulate (BA24), but not medial

prefrontal, whereas 'other' versus 'syllable' yielded activation in the left medial frontal (BA8/9/10), amongst other regions.

Thus, whereas a medial prefrontal role in self-referencing was established, it became also clear that the role extended to "other-referencing", in line with research into perspective taking and theory of mind (Frith & Frith, 1999). Maddock et al. (2001) correspondingly hypothesised its function to include "social and emotional processes associated with the mental representation of intimately familiar people" (p.673). Interestingly, there is a strong positive reinforcement component involved in orbitofrontal memory processing (Baxter et al., 2000; Elliott et al., 2000). In line with this, clinical evidence indicates that damage to ventromedial prefrontal cortex disrupts goal-directed actions that are guided by motivational and emotional (conditioned) factors (Gallagher et al., 1999). This role of ventromedial prefrontal cortex in self-relevant memories will be of importance with regard to the study introduced in Chapter 9, in which recognition of personally known faces was contrasted with recognition of famous faces.

Temporoparietal junction

From the role of the parietal cortex in the translation from ego- to allocentric spatial representations and between different egocentric representations (e.g. Andersen et al., 1985, see Introduction to Part I, Chapter 2), Burgess et al. (2002) derive a role for this area also in episodic memory. The idea is that representations stored in the hippocampus are (as in spatial memory) view-point independent, but that for retrieval into working memory/ imagery a specific perspective is required. According to Burgess et al. (2002) information about events, stored in the form of an index-like code in the hippocampus, is used to generate an allocentric representation of locations of elements of the scene of the event in the parahippocampal gyrus. The role of the posterior parietal cortex is seen in the successive translation from allocentric to body-centered and then head-centered representations. This is consistent with anatomical connections of the posterior parietal areas (BA7, Andersen, 1997). Further corroborating this hypothesis, a single unit study implicated BA7 in allocentric-egocentric translations (Snyder et al., 1998).

Retrosplenium and precuneus

Retrosplenial cortex and precuneus are very frequently activated in neuroimaging studies of memory (Addis et al., 2004; Burgess et al., 2001b; Cabeza & Nyberg, 2000; Fletcher et al., 1995; Maguire et al., 1999; Maguire et al., 2000; Maguire & Mummery, 1999; etc., see Maguire, 2001a for an overview).

The caudal posterior cingulate cortex (including the retrosplenial cortex, BA29, within the callosal sulcus, and BA30 extending from the callosal sulcus onto the convexity of the cingulate gyrus, Braak, 1979; Vogt et al., 1995, in Maddock, 1999) is linked by strong reciprocal pathways to dorsolateral prefrontal and anterior cingulate cortices and the anterior and lateral thalamic nuclei. It may serve to connect the dorsolateral prefrontal cortex with the hippocampal formation (e.g. Goldman-Rakic et al., 1984; see Maguire, 2001b). Strong efferent connections from the retrosplenial cortex to the parahippocampal and entorhinal cortices provide another means by which the retrosplenial cortex could influence episodic memory processes (Suzuki & Amaral, 1994, in Maguire, 2001b). There are further connections with the superior temporal sulcus and posterior parietal cortex (Morris et al., 1999a). BA31 includes both posterior cingulate and precuneate cortices, and the two regions are reciprocally connected (Baleydier & Mauguiere, 1980; Morris et al., 1999b; Van Hoesen et al., 1993, in Maddock et al., 2001). Fletcher et al. (1995) hypothesised that this region may be associated with visual imagery in conscious recall. Precuneus has additionally been observed to be active in memory involving auditory and motor imagery (Ogiso et al., 2000; Zatorre et al., 1994), and may thus have a role in poly-modal imagery associated with successful memory retrieval.

According to Maddock (1999) the posterior cingulate takes an "evaluative" role in emotional and motivational processing as compared to an "executive" role of the anterior cingulate. However, patients with lesions primarily involving retrosplenium are not notable for emotion-related deficits, but rather for significant memory problems (e.g. Bowers et al., 1988; Rudge & Warrington, 1991; Valenstein et al., 1987; see Maguire, 2001b and also Vogt et al., 2000). One potentially significant aspect with regards to patients with retrosplenial amnesia is that most have bilateral or left retrosplenial lesions

(Maguire, 2001b). This is concordant with our hypothesis of left-lateralisation of the medial temporal lobe involvement in episodic memory. It might thus be that inputs to the medial temporal regions are similarly lateralised. It has been discussed in the Introduction to Part I (Chapter 2) that impairment of the *right* retrosplenial cortex by contrast is correlated with topographical disorientation. From that role of the retrosplenial cortex as a transition zone between egocentric inputs from areas such as posterior parietal cortex, and head direction and ultimately allocentric processes in the medial temporal region, Burgess et al. (2002) hypothesise that the continuous strip of activation seen between the parahippocampus and precuneus, including retrosplenial cortex, may reflect the buffering of successively translated representations of the scene of the event (from allocentric to body- to head-centred, see above). This is in line with visuospatial and proprioceptive functions in the monkey posterior cingulate. There, neurons show responses that are correlated with eye-gaze angle and the size and direction of eye movements (Olson et al., 1996). However, this function seems to refer largely to visualisation rather than vision.

In sum, the posterior cingulate area appears to be one of the most important relays in the retrieval network of hippocampal memory, affording imagery and allo- to egocentric translations for the successful recovery of a memory.

Cerebellum

The role of the cerebellum in episodic memory has not been captured clearly to date. However, in addition to the well established motor function of the cerebellum (Brooks & Thach, 1981; Ito, 1984, in Gao et al., 1996;), recent clinical and neuroimaging studies revealed a role in non-motor behaviours (e.g. Kim et al., 1994). These involve judging the timing of events, solving perceptual and spatial reasoning problems, including mental rotation of abstract objects, and generating words according to a semantic rule (see Andreasen et al., 1999, and Gao et al., 1996 for overviews).

Mainly the ventral part of the cerebellum, projecting to prefrontal areas (BA46 and 9 in the monkey) via the thalamus (Middleton & Strick, 1994, in Leiner et al., 1995)

apparently evolved uniquely and enlarged enormously in the evolution of the human brain. Additionally, it has been found that the cerebellar dentate nucleus in humans can target Broca's area (see Leiner et al., 1995). In Leiner et al. (1995)'s view, the cerebro-cerebellar circuitry performs repeated transformations on motor, cognitive or language tasks, leading to tasks becoming automatised and thus faster. A further hypothesis concerns a cerebellar role in subvocal speech, in line with lateral (and medial) cerebellar activation during auditory-verbal tasks and silent counting and imagery (see Leiner et al., 1995 for an overview). Gruber (2001) showed right cerebellar activation associated with verbal working memory tasks, together with left-hemispheric speech areas including Broca's area (BA 44), lateral and medial premotor cortices, as part of the 'phonological loop'. Importantly, this activation disappeared when silent articulatory suppression prevented subjects from phonological rehearsal. However, results from a PET study showed additional activation in an inferior and lateral part of the cerebellum during a rule-based word generation task that was spatially disparate from that found during speech (Petersen et al., 1988; Petersen & Fiez, 1993). Finally, Andreasen et al. (1999) argue that cerebellar activation found in a PET activation -"pure thought"-experiment, is part of an interactive network between the mainly right-hemispheric cerebellum and contralateral prefrontal cortex engaged in planning, initiating and coordinating the conscious retrieval of time-linked memory. In that experiment, subjects intentionally recalled a specific autobiographical memory experience. The possibility of subvocalisation was controlled for. The authors hypothesise that the cerebellum provides a common stratum that serves many types of mental activity involved in operating multiple independent timing processors (Keele & Ivry, 1990) or combining simple cognitive units into larger units and linking them to a triggering context (Thach, 1998; in Andreasen et al. 1999).

In sum, the function of the cerebellum possibly extends to the fine coordination of not exclusively motor tasks.

I have thus discussed the possible respective roles of the brain areas involved in the episodic memory retrieval network. This will be of relevance for the interpretation of

neuroimaging data presented in Chapters 9 and 10. The next section focuses on the characteristics that distinguish everyday memory or autobiographical memory from laboratory-generated episodic memory. At its base there might be another answer for a lack of hippocampal activation formerly found in neuroimaging experiments of episodic memory.

The difference between autobiographical memory and laboratory-based episodic memory

This section introduces neuroimaging experiments that have previously assessed natural, real-world, personal autobiographical memories. The focus lies on the differences between such memories and their underlying neural representation and laboratory-generated episodic memories. Maguire (2001a) summarises that the direct comparison between the retrieval of autobiographical events, as opposed to general event memories indeed revealed left hippocampal activation (Maguire et al., 2000; Maguire et al. 2001a, 2001b; Maguire & Mummery, 1999). It further showed activation in the medial frontal cortex (BA 10), in line with the discussed involvement of this area in the processing of 'self'-relevant information. The paradigm used in these studies involved interviewing the subjects several weeks prior to scanning. Like this, personal memories and general knowledge were sampled from across 20 or more years up to very recent memories. In the scanner, subjects heard sentences and responded by key press if they were true or false.

A more recent experiment also opposed neural activations of the retrieval of autobiographical to that of laboratory material (Cabeza et al., 2004). Undergraduate students first took photos in specified campus locations, viewed in the laboratory similar photos taken by other participants and were then scanned while recognising the two kinds of photos. The "autobiographical" condition elicited greater activity in medial prefrontal cortex, more precisely showing less deactivation for the "autobiographical" condition. Further regions showing stronger activation in the "autobiographical" condition included bilateral visual and right parahippocampal regions, and bilateral

subiculum. There is thus evidence for a stronger hippocampal involvement in episodic memories with a stronger connection to the self.

Another recent fMRI experiment further investigated how autobiographical event memories were modulated by the parameters detail, emotion, personal significance and recency (Addis et al., 2004). Similarly to Maguire's paradigm, see above, participants retrieved temporally specific autobiographical events and general repeated autobiographical events cued by a title that they had provided together with the memory prior to scanning. Participants additionally provided information about memory detail, emotion, and other aspects. Results from the parametric modulation analysis of specific autobiographical memories revealed an effect of detail and personal significance in the medial temporal lobe bilaterally, and additionally of recency on the right. The level of emotionality did not modulate medial temporal lobe activation when recency was taken into account and when personal significance was entered as a covariate, the parametric effect of recency dissipated. Thus, recency, emotionality, and personal significance all seem to play a significant role in medial temporal lobe activation upon autobiographical event memory. However, it appears hard to disentangle the effect of each of these factors from the others. In the following two sections, the discussion of the correlation between hippocampal involvement in episodic memory and memory age on the one hand, and between the hippocampus and emotional memories on the other hand is given some more space.

The effect of memory age on hippocampal activation in autobiographical memory

On the one hand autobiographical memories usually differ from laboratory-generated episodic memories in that they are much older and more consolidated. On the other hand, Addis et al. (2004), see above, found hippocampal activation in memory retrieval to correlate with recency. Within memory research there is a vivid debate about the relationship between memory age and the hippocampus. Rempel-Clower et al. (1996) reported that the length of temporal gradients of enduring retrograde amnesia correlated with the increasing extent of hippocampal damage. Some autobiographical memories

were found to be retained in people with hippocampal complex lesions if these had been acquired decades earlier (Reed & Squire, 1998). This is congruent with classical consolidation theory that suggests limited hippocampal involvement in memory retrieval (Marr, 1971; Squire & Alvarez, 1995). However, the consolidation time estimated in these cases goes well beyond the time-frame initially postulated for consolidation to occur. Moreover, other studies have failed to reliably replicate the above pattern of time-dependent memory loss. They investigated the degree of hippocampal involvement in memory functions in lesioned animals and in human patients with medial temporal lobe damage (see Piefke et al., 2003, for an overview). For example, Cipolotti et al. (2001) reported extensive and basically ungraded retrograde amnesia in patient V.C., who presented with gross abnormalities in both hippocampi but normal entorhinal and extrahippocampal cortex volumes bilaterally. In view of the inconsistent findings, an alternative model for long-term memory consolidation has been proposed:

Nadel and Moscovitch's (1997) multiple trace theory posits that retrieval of contextually rich memories remains hippocampal-dependent over time. According to the multiple trace theory each reactivation of a memory leads to the creation of a new memory trace, each of which is assumed to involve an ensemble of hippocampal and neocortical neurons. The growth of memory traces occurring with repeated reactivation of each of the memories is supposed to render older memories less susceptible to disruption from hippocampal damage than recent ones. Distinct types of retrograde amnesia may result depending on the location, type and extent of medial temporal damage.

Recent neuroimaging studies can be considered in the search for evidence in support for this theory. For example Maguire and Frith (2003) contrasted recent versus remote autobiographical memories, matched for level of detail, and yielded right hippocampal activation. This is congruent with Addis et al.'s (2004) finding reported above. Piefke et al. (2003) also reported retrieval of highly recollective recent autobiographical memories to be associated with increased hippocampal activation bilaterally relative to less recollective remote autobiographical memories. By contrast, others did not report such a difference (e.g. Conway et al., 1999; Graham et al., 2003, study 1; Maguire et al.,

2001a; Ryan et al., 2001). Graham et al. (2003, study 1) found no difference in activation patterns between a recent (past 5 years) and a remote (childhood or adulthood) memory retrieval cued by a word in a group of elder subjects (mean 60.4 years). Maguire et al. (2001a) found no parametric effect related to memory age in the hippocampal regions.

In an fMRI study, in which participants aged between 50 and 72 years were asked to recollect autobiographical events from an events list that occurred either within the last 4 years or more than 20 years ago, Ryan et al. (2001) found equivalent levels of hippocampal activation in both conditions in all 10 participants.

Further in line with these findings, Gilboa et al. (2004) found the hippocampus to participate equally in retrieval of both remote and recent memories. However, an important criterion for hippocampal modulation was memory vividness. In this study, middle aged participants were scanned while they viewed photographs depicting not well-rehearsed events of their own lives from each of five time periods, ranging from when the participants were 5 years old to the present time (collected from relatives and friends). Each picture was presented for 30s to allow participants to reconstruct and fully re-experience the memory. While hippocampal activity was comparable in retrieval of vivid remote and recent memories, there was a greater distribution of activation along the hippocampus in remote memories than in recent memories. Thereby the retrieval of detailed vivid autobiographical experiences as opposed to personal semantic information was found to be a crucial mediating feature determining the involvement of hippocampus (as well as precuneus and lingual gyrus).

In conclusion, firstly, it seems that it may be hard to conclusively corroborate the multiple trace model using neuroimaging since two opposed influences of memory age modulate hippocampal activation. On the one hand, the more recent a memory, the more fragments of the memory trace might be retrieved and thus the stronger a signal might occur. On the other hand, the older the memory trace, the more often re-encoding has taken place and possibly the wider distributed the trace is in the hippocampus.

Intriguingly, Gilboa et al. (2004) succeeded in showing this very pattern of more distributed hippocampal activation in (well preserved) remote memories.

Secondly, memory vividness appears to be the underlying modulator of age-dependent hippocampal activation in autobiographical memory.

Emotional memories and the hippocampus

It could be argued that vividness is further correlated with emotional saliency. Generally, personally significant autobiographical memories are also more emotional than memories without personal relevance. There are two pathways considered to influence memory consolidation for emotional events (Cahill & McGaugh, 1998). One involves stress-hormones adrenaline and cortisol that are released after the occurrence of an emotional event (see Cahill & McGaugh, 1998, for a detailed discussion of the mechanisms involved). Another has been discovered through studies involving electrical stimulation of the amygdala which resulted in (aversive) emotional learning (Goddard, 1964). It is known that also in humans, long-term, emotionally influenced memory is impaired in patients with selective amygdala damage (e.g. Cahill et al., 1995), whereas memory for relatively unemotional material is normal in these patients. The amygdala is seen as the site of modulation of memories formed in the hippocampus and entorhinal cortex. Electrophysiological evidence strongly suggests that influences from the basolateral nucleus of the amygdala modulate long-term potentiation in the dorsal hippocampus (Ikegaya et al., 1996). In line with this, in humans, bilateral amygdala activity during memory encoding was found to correlate with enhanced episodic recognition memory for both pleasant and aversive visual stimuli relative to neutral stimuli (Hamann et al., 1999). Further, a recent study by Strange and Dolan (2004) showed that the successful encoding of emotional verbal stimuli was related to increased amygdala activation. Items that evoked amygdala activation at encoding subsequently evoked greater hippocampal responses at retrieval. If the enhanced amygdala encoding was neurochemically prevented, hippocampal retrieval effects also ceased.

Thus, autobiographical memories with more emotional context compared to laboratory-based episodic memories may yield stronger hippocampal activation through modulatory influence from the amygdala. We keep this in mind for the discussion of the results from the fMRI study in Chapter 7 that involved photographs of participants' friends as stimuli.

The last section of this chapter introduces the characteristics of olfactory memory. This prepares for two studies; experiment 2 of Chapter 8, and Chapter 10, using olfactory context to study the multimodal aspect of real-world episodic memories.

Olfactory memory

Two arguments have led to the exploration of episodic memory retrieval via an olfactory cue. The first is the old idea of the hippocampal role as a 'convergence zone' (e.g. Alvarez & Squire, 1994; Damasio, 1989a; Moll & Miikkulainen, 1997), linking information from different sensory modalities that are represented in disparate cortical areas. Some authors have suggested that the hippocampus provides a means of forming associations between information presented in different modalities or stored in different brain regions (Marr, 1971; Mayes et al., 2001; Squire & Zola-Morgan, 1991), cross-modal associations being indeed one of the few aspects of recognition memory seemingly impaired after restricted hippocampal damage (Mayes et al., 2001; Vargha-Khadem et al., 1997).

Secondly, olfactory cues have also been seen as particularly potent reminders of past experiences. Proust's description "no sooner had the warm liquid, and the crumbs with it, touched my palate than a shudder ran through my whole body, and I stopped, intent upon the extraordinary changes that were taking place....", (Proust, 1922/ 1960 transl. , p.58) formed the basis for what has been investigated as the 'Proust phenomenon', the ability of odours to spontaneously cue highly vivid and affectively toned autobiographical memories which reach a long way back (Chu & Downes, 2000). However, scientific evidence in favour of the 'Proust phenomenon' is scarce (but see Chu & Downes, 2002; and Herz et al., 2004) or even contradicting it (e.g. Bolger & Titchener, 1907; Davis, 1975; Herz, 1998; Rubin et al., 1984). This is on the other hand

in line with the reported unreliability of the sense of smell in humans, which manifests in poor odour-recognition memory (Engen & Ross, 1973) and odour-identification (Cain, 1979; Engen, 1987; Lawless & Engen, 1977; see Schab, 1991, for a review). It has been found that the same odour tended to be encoded differently on successive presentation (Cain, 1979). Further, participants probed with the odour of a wrong label that they attributed in a former session readily fell for the lure and falsely recognised the bait (Cain & Potts, 1996). Furthermore, odour perception has been found to significantly rely on visual cues (Gottfried & Dolan, 2003) or verbal labels (Lyman & McDaniel, 1990; Rabin & Cain, 1984, etc., see Herz & Engen, 1982, for a review). In spite of these findings concerning human odour perception, the hypothesis of the potency of odours as memory cues remained strong, possibly nurtured by vivid personal anecdotes of the kind: "This smell reminds me of standing on the deck of my grandfather's yacht when I was about eight". In an attempt to capture this phenomenon, Rubin et al. (1984) argued that long term retention in olfactory memory could be due to odour cues to memory suffering from less interference than verbal cues during the retention interval. This hypothesis is supported by evidence for reduced retroactive interference in olfactory memory (Lawless & Engen, 1977) and can further explain the recently claimed "proof" of the 'Proust phenomenon' by Chu and Downs (2002) and Herz et al. (2004).

In summary, thus, although odour may not be the most efficient cue to memory, it may still play an intriguing and significant role. It further allows us to investigate issues relating to genuinely cross-modal stimuli in episodic memory. Including an odour cue in our virtual reality paradigm in Chapter 8 we sought to further investigate our initial findings on binding of various aspects of an event into an episode. In Chapter 10 we investigated the neural bases of memory for spatial versus olfactory context in order to highlight modality-specific and modality-transcending neural activity in episodic memory retrieval using fMRI.

Chapter 8) Binding of context and content in hippocampal-dependent episodic memory

Introduction

This study investigates the binding of the context of an event with the event's content in episodic memory (Trinkler et al., in press). For instance, if I remember that we once had a discussion about nanobots over lunch, will I remember all the contextual aspects of it, i.e. the location, the date, who was present, and what we had for lunch, as an encapsulated whole, or do I retrieve single aspects only?

In both, Experiment 1 and Experiment 2, a series of pseudo-realistic events were simulated using a virtual reality paradigm (see King et al., 2004). The memories for various aspects of these events was subsequently probed. This procedure combines the contextual richness of real autobiographical memories with standardisation of stimuli across subjects as achieved in traditional laboratory experiments on episodic memory. During the experiment, participants moved through a virtual reality town and encountered virtual characters within it. An event consisted of the presentation of an object to the participant by the virtual character (see Fig. 8.1). The receipt of an object marked the content of an event in contrast to the ongoing context of the event, including the surrounding spatial environment, and the person giving the object (Burgess et al., 2001b).

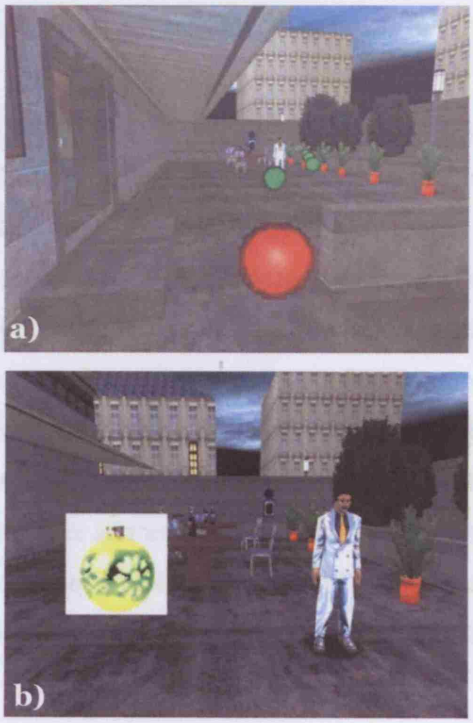


Figure 8.1 Snapshot of the encoding phase of Experiment 1 and 2. The participant follows a trail of green dots (a), (the next dot to move over is coloured red), encounters a distinct person in a distinct location, and is presented with the image of a distinct object (b).

In Experiment 1, after the learning phase, participants were tested on their memory for the events using a context-dependent two-alternative forced choice paradigm: Pairs of objects were presented in a particular place, with a particular character present, see Fig. 8.2. Two types of questions probed memories for the different elements of context; "Which object did you receive in this place?" and "Which object were you given by this person?". In addition, one question-type tested memory for the event-content, i.e. of the object given. In this condition, the familiar object had to be recognised compared to a similar-looking novel foil.

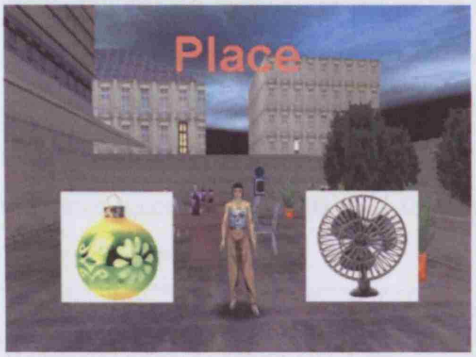


Figure 8.2 An example of a context-dependent paired forced choice question from Experiment 1. Shown is the 'place'-question: "Which object did you see in this place?"

As mentioned in the Introduction to Part II (Chapter 7), this experiment has also been used to test hippocampal-dependence of context-dependent as opposed to familiarity-based recognition memory, (see King et al., 2004). In the study presented here, the scope was to investigate the relationships between the retrieval probabilities of different elements of the same event. For example, in the event illustrated in Fig. 8.1, we asked whether if participants retrieved the bauble correctly when probed with the man in the suit, would they also retrieve that bauble when probed with the place (terrace café). This was addressed testing the performance data against two theoretical models using contingency tables. Under a fully dependent model, retrieving one element of an event is maximally correlated to retrieving another element of the same event, see Table 8.1.

	Retrieval with one cue (more successful)	
Retrieval with another cue	**Proportion correct (f)**	**Proportion incorrect (1-f)**
Proportion correct (p)	a = p	b = 0
Proportion incorrect (1-p)	c = f-p	d = (1-f)

Table 8.1 Contingency table for a fully dependent model.

Under a fully independent model, retrieving one element of an event is independent of retrieving another element of that event, see Table 8.2. In the dependent model, if one retrieval cue is more successful than another, then both cues should be successful every time the least successful is, hence cell ***a*** (proportion correct for both questions) represents the proportion correct of the least successful (***a*** = p). Also, there should be no cases where the least successful is correct and the more successful incorrect, hence cell ***b*** = 0. Further, all incorrect cases of the more successful cue (1-f) must occur in the case where neither cue is successful, cell ***d*** = 1-f. Finally, cell ***c*** expresses the case where only the more successful cue retrieves the correct answer (***c*** = f-p).

	Retrieval with one cue (more successful)	
Retrieval with another cue	**Proportion correct (f)**	**Proportion incorrect (1-f)**
Proportion correct (p)	***a*** = p*f	***b*** = p *(1-f)
Proportion incorrect (1-p)	***c*** = f *(1-p)	***d*** = (1-p)* (1-f)

Table 8.2 Contingency table for the independent model.

In the independent model, the proportions of ***a, b, c*** and ***d*** can be estimated by combining the assumed probabilities of correct and incorrect cases of two cues, see Table 8.2. This procedure has been piloted before (Spiers, 2002; see also Trinkler et al., in press) using a former version of the virtual reality paradigm, as briefly introduced in the Introduction to Part II (Chapter 7). First results had cast doubt on the suggestion that events are encoded holistically, as a very good fit of the data was provided by a model assuming an independent probability of success in retrieving the same event from different contextual elements. The former study had however yielded generally low levels of performance and differences in retrieval probabilities between different cues (place versus person). Thus, a high degree of guessing could have obscured some possible dependencies in the data. Furthermore, the high degree of interference caused in the experiment using only two characters and two places to provide 16 different events, may have resulted in recollection being less 'truly episodic' in Tulving's sense of fully re-experiencing distinct events (e.g. Tulving, 2002, see Introduction to Part II, Chapter 7). Similarly, the re-use of contextual cues in different events might prevent

simple use of a fragmentation model such as that in Jones (1976), as discussed by Wagenaar (1986). These considerations prompted the following study.

Experiment 2 extended the findings from Experiment 1 in two ways. On the one hand we additionally looked at recall of event-content, cued by different context-cues. This allowed us to directly investigate the possibility of retrieval-hierarchies, i.e. whether different context-elements would lead to different retrieval-probabilities. On the other hand, one more contextual element was introduced, namely an olfactory cue.

Experiment 1

Participants

12 male participants took part in this experiment, age range = 21-28, mean age 23.4, mean IQ 114 (inferred from Ravens' Matrices norms for UK, Raven et al., 1994, table APM XII p.69), mean score 10.43, standard deviation = 1.22).

Encoding task

A virtual reality town, built on the commercially available computer game Deus Ex, provided the environment for the test. It was presented on an AMD Athlon XP2200 computer with a standard 19 inch monitor at a resolution of 800x600 pixels and a vertical refresh rate of 60Hz. To manoeuvre within the town, participants used the cursor keys of the keyboard and followed a trail of green icons, see Fig. 8.1a. In distinct places along the route, participants encountered virtual characters who presented them with an image of an object (display size 7x7 cm), see Figure 8.1b. Subsequently, a new trail of icons would appear for the participant to follow to the next encounter. Participants were told that they would be tested on these events afterwards and instructed to try and remember the person, object and place of each event. All participants experienced the same sequence of 20 events (rather than counterbalancing order, objects etc.) as the data were also used to assess the memory performance of patient Jon (see King et al., 2004). The encoding phase took about 15 minutes on average.

Recognition Task

Immediately after the encoding task, participants were given paired forced-choice recognition tests on all aspects of all events (3x20 tests). They were presented with two objects, on the left and right of the screen, a virtual character in the foreground and a snapshot of one of the locations in the background. A word appearing at the top of the screen indicated what type of event information was being probed (see Fig. 8.2). Two questions probed context-dependent memory ('place' and 'person') and one question ('object') probed recognition of the content of the events. Participants responded by button press, indicating whether the left or the right object was associated with the cue in question. In the 'object' condition, the foil object was a similar looking version of the original image that had been presented in the encoding task. At the same time, the virtual character and the location in which the two objects were shown had to be ignored.

Practice Trial

Prior to testing, participants were given a trial run of both the encoding task (consisting of 3 events presented in an alternative virtual reality town) and the recognition memory test.

Results

	Question-type		
	Context-free	**Context-dependent**	
	Object	**Person**	**Place**
Average retrieval performance	86%	83%	84%
(standard deviation in brackets)	(6%)	(12%)	(9%)

Table 8.3 Average retrieval performance of 12 participants in Experiment 1, per question type (King et al. 2004).

The average performance over all participants is shown in Table 8.3. Note that average performance does not differ between the different question types. The performance data was used to construct contingency tables for each participant individually using Fisher's exact test. The independent model assumed by Fisher's exact test was far from being

rejected, see Table 8.4. Given approximately equal performance across conditions, the dependent model could be modified to include guessing, as illustrated in Table 8.5.

Participant number	P value Object vs. Person	P value Object vs. Place	P value Person vs. Place
1	1.00	1.00	1.00
2	0.85	0.72	0.90
3	0.49	0.40	0.25
4	0.63	0.40	0.60
5	0.63	0.38	0.63
6	1.00	0.81	1.00
7	0.63	0.80	0.90
8	0.08	0.63	0.34
9	0.02	0.28	0.52
10	0.21	0.34	0.61
11	0.80	0.75	0.72
12	0.75	0.80	0.72

Table 8.4 P-values (Fisher's Exact Test) for h_0 = Rejection of independent model per participant and event-element-pairing in Experiment 1. There is no sign of similarity in performance on different questions about the same event. Note that, for the given performance levels (e.g. 0.85), a fully dependent model with guessing (see Table 8.5) would score p=0.15 – i.e. there is not enough power to reject the independent model at p<0.05. However, the average p-values are clearly greater than 0.15, consistent with an independent model.

	Retrieval with one cue	
Retrieval with another cue	**Proportion correct** ($p = p' + g/2$)	**Proportion incorrect** ($1 - p$)
Proportion correct ($p = p' + g/2$)	$a = p' + g/4$	$b = g/4$
Proportion incorrect ($1 - p$)	$c = g/4$	$d = 1 - p' - 3g/4 = g/4$

Table 8.5 Contingency table for a fully dependent model with guessing in the case of equally good retrieval via either cue. The proportion correct is p in both cases. The proportion of events in which both cues are correctly retrieved from memory is p', the proportion of guessed answers is g. All responses are either due to correct retrieval of both aspects or due to random guessing, i.e. $p' + g = 1$.

	Independent model	Dependent model with guessing
Comparison	**P value (χ^2, df=1)**	**P value (χ^2, df=1)**
Object vs. Person	0.92 (0.009)	<0.0001 (28.2)
Object vs. Place	0.23 (1.461)	<0.0001 (39.2)
Person vs. Place	0.099 (2.717)	<0.0001 (15.2)

Table 8.6 P-values and Chi Square statistics for both, the comparison of data with the expectation according to the independent model and the dependent model with guessing over all participants (n=240). The dependent model can be clearly rejected whereas the independent model provides a reasonable fit.

Contingency tables were created as expected under either model on the basis of the frequencies of each type of paired response (e.g. correct-correct, correct-incorrect, etc.) for the 20 events. The Chi Squared Test applied to a contingency table over all participants corroborates data from the single participants' analysis, see Table 8.6. The dependent model including guessing is rejected at $p<0.0001$ for all comparisons. On the other hand, the independent model provides a good fit. Moreover, in a direct comparison between the two models, for all three pairs of questions the sum of squared differences between model and data is significantly smaller for the independent model than for the dependent model with guessing, see Table 8.7. In summary, evidence is in favour of event aspects being retrieved independently.

	Mean squared difference (over participants, stdev. in brackets) **between data and..**		P-value (t-test of mean squared diffs)
Comparison	**..independent model**	**..dependent model with guessing**	
Object vs. Person	0.0018 (0.0003)	0.0065 (0.0003)	<0.005
Object vs. Place	0.0007 (5.6×10^{-5})	0.0062 (0.0003)	<0.001
Person vs. Place	0.0004 (6.6×10^{-5})	0.0031 (0.0002)	<0.005

Table 8.7 Direct model-data comparison. For all three comparisons the mean squared difference $((a-a')^2+(b-b')^2+(c-c')^2+(d-d')^2)/4)$ between model and data is significantly smaller for the independent model than the dependent model with guessing.

Discussion

The results of Experiment 1 support a model where all elements of an event are encoded and retrieved as independent pair-wise associations. However, there is one remaining caveat interpreting the results from Experiment 1, concerning the possibility that in the instant of retrieving the information about the person, the whole event is successfully retrieved, but that at the instant of retrieving the information about the place, no element is retrieved. Thus, the simple cued-recognition paradigm only allows us to conclude that events are not *encoded* holistically – otherwise variations in the strength of encoding of different events would produce some dependencies among the performance of the different questions concerning the same event. However, it is still possible that events are *retrieved* holistically, because a separate retrieval process is required for each question regarding a given event. To address this issue, in Experiment 2 a cued-recall test was added, in which memory for different elements of an event could be probed simultaneously.

Experiment 2

In this experiment, the virtual reality paradigm used above was modified to test *cued recall* in addition to forced choice recognition of context-object pairs and familiar objects. After the encoding phase, participants were additionally presented with the individual components of all events and asked to reconstruct the events they experienced. This allowed us to investigate possible "retrieval-hierarchies", i.e. whether some contextual cues may be preferred over others to retrieve information about an event. Furthermore, an additional contextual element was added: Each virtual reality-event includes a distinct olfactory cue in addition to distinct people and places. This allows an exploration of differences in retrieval cues and binding dependent on cue-modality.

Participants

12 subjects participated in the experiment, 5 females and 7 males, with an average age of 28 years (ranging from 22-39), and Raven's score of 9.75 (standard deviation = 2.0) equivalent to an IQ of 108 as estimated according to the Ravens' Matrices norms for UK

(Raven et al., 1994, table APM XII p.69). Only people who rated their sense of smell 5 or above were included (self-rating, on a scale from 1 to 7).

Encoding task

The virtual town, computer and manner of navigating and responding were identical to Experiment 1. In distinct places along the route, subjects met virtual characters who presented them with an object. Simultaneously with the occurrence of the object, the experimenter also presented an odorous stimulus from a phial (about 1cm from the subject's nose) for the duration of one sniff. Then, subjects continued their journey through the virtual town along a new trail of green icons. Subjects were told that they would be tested on these events subsequently and instructed to try and remember the person, object, place and odour from each event. In contrast to Experiment 1, each subject experienced a *unique composition* of 10 events, that is, assignment of objects and people and places and odour was randomly varied between subjects. There were 5 different possible first places that were always reached from the same arbitrary start location within the town and the sequence of locations was the same for all subjects. The whole "encoding-walk" took subjects about 15 minutes on average.

Odour stimuli

Odours were presented in medicine bottles labelled with numbers visible to the experimenter only. Through extensive pilot experiments odorous liquids had been selected that were rated neutral in hedonic quality, were matched in perceived intensity, and easily distinguished from one another. They were rated as familiar and could be described verbally, e.g. 'rose', 'peanut butter', 'white spirit', 'spearmint', etc.

Practice trial

Prior to testing, participants were given the same trial run as in Experiment 1 with the addition of an odour cue for each event.

Pre-experimental exposure to olfactory stimuli

After participants had conducted the practice trial, they were presented with the 10 phials used in the experiment, and asked to sample all smells, one after another, and to verbally describe them. If participants failed to come up with a label, they were given a hint (e.g. "is it a flower?") and further prompted until they had a specific label for each of the ten odour stimuli.

Recognition test

After the encoding task, as in Experiment 1, participants were given paired forced-choice recognition tests: A question word on the screen preceded the presentation of two objects on the left and right of the screen, together with one cue according to the question word: In the 'place' condition, the two objects appeared in front of a snapshot of one of the 10 events-locations, in the 'person' condition, one of the 10 characters appeared between the two objects in front of a plain brown background (illustrated in Fig. 8.3), in the 'odour' condition, the subjects were presented with one of the 10 odours from a phial together with the visual presentation of two objects in front of a plain brown background. Subjects indicated by button press, whether they had received the left or the right object in the presence of the respective cue. For the 'object' condition, an object from the encoding phase was presented together with a similar looking new lure in front of a plain brown background.

Figure 8.3 Experiment 2: Example of visual stimulus in the 'person' condition. The participants answered which of the two objects (left or right) had been presented by the person.

Cued recall test

After the recognition memory task, subjects were shown randomly arranged laminated paper-copies of all elements of the events they had experienced in the encoding task: virtual characters, images of objects and snapshots of locations. The odour stimuli were presented on commercially used test-strips on pegs. Subjects were instructed to try and reconstruct as much as possible "what they could remember went together". They were further told that their reconstruction process would be coded on-line by the experimenter. Which card/odour-clip was put together with which other card/clip and in what sequence was recorded. Subjects were allowed to finish before they had recombined all single elements, when they felt they could not remember anything more. Finally, subjects were asked what strategies they had used to encode the events.

Results: Recognition test

Fig. 8.4 shows the results of the recognition memory test in Experiment 2. Performance on the object question was significantly greater than performance on any other question type (repeated measures ANOVA, $F_{3,33}$= 16.41, $p<0.001$, single comparisons between object and any other condition, one tailed t-tests, all $p<0.001$) and better than in Experiment 1, probably because of the smaller number of events used. Within the context-dependent question types, there was an effect of question types (repeated measures-ANOVA, $F_{2,22}$= 4.02, $p<0.05$) performance was significantly higher for the 'person' question than for either 'place' or 'odour' questions (paired t-tests, one-tailed, $p<0.01$ for 'person' vs. 'odour', $p<0.05$ for 'person' vs. 'place'), but there was no significant difference between 'place' and 'odour' questions ($p=0.17$). Regarding the odour cue, a possible relation between recognition memory score and odour identification ability was assessed: Odour identification as assessed pre-experimentally was estimated 1 for a correct label, 0.5 for an approximate description and 0 for no description. There was no correlation between individual *subjects'* identification scores and their memory scores for odour-cued recognition (R^2=0.0048), however, there was a high correlation between an *odour*'s identification score over all subjects and how well it elicited odour-cued recognition (R^2=0.80).

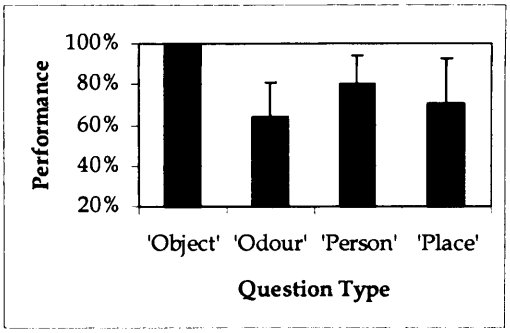


Figure 8.4 Experiment 2: Average performance in the paired forced-choice recognition memory test, by question type. N=12, error bars show standard deviation.

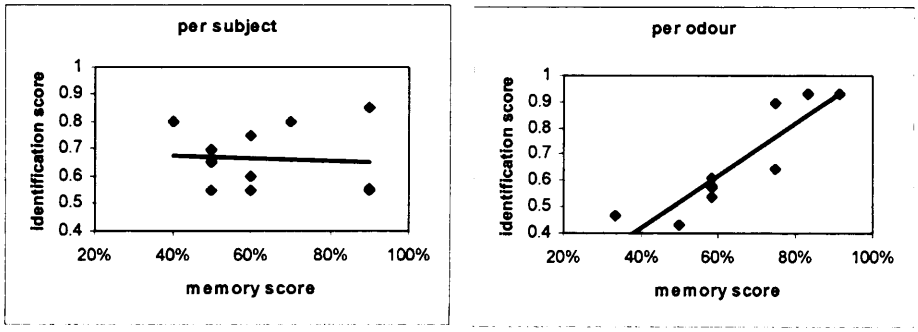


Figure 8.5 Experiment 2: Relation between odour identification score and memory performance, per subject and per odour.

Results: Cued recall

Data from subjects' reconstruction processes were scored as follows: Subjects were allowed to continue reconstructing one event after having attempted to reconstruct another event in the meantime, and made frequent use of this possibility. On the basis of such data, all subjects' reconstructions of all 10 events were scored in two ways. Firstly, the number of elements of an event a subject correctly put together in the first attempt, before going on to reconstructing another event, was counted. This is referred to as the 'initially remembered' score. Secondly, the number of elements of an event subjects had correctly put together at the end of their reconstruction process was counted. This is referred to as the 'eventually remembered' score. Overall, for 'initially remembered' items, 66% of all events (total = 10 events x 12 subjects) were at least partially correctly reconstructed as opposed to 34% of events of which no two elements were correctly matched. For 'eventually remembered' items, these percentages amounted to 81% at least partially correctly reconstructed events versus 19% entirely forgotten (see Table 8.8).

No. of combined elements remembered	**Initially remembered**		**Eventually remembered**	
4 elements	7%	} 66%	19%	} 81%
3 elements	18%		29%	
2 elements	41%		33%	
<2 elements (i.e. forgotten)	34%		19%	

Table 8.8 Experiment 2, cued recall task: Proportions of correctly remembered elements over all events and all participants.

The percentage of events of which all 4 elements were remembered together correctly does not exceed 19%. The full retrieval of a complete event is thus rare compared to the retrieval of the object via a single cue in the recognition test (which was 64% for the worst case, odour). Table 8.9, showing *which* elements were not recombined with the others correctly when the other 3 elements were correctly matched, reveals that the association with odour was the weakest over all: It could not be reattributed to the other elements of an event in 91% of all cases that missed one element. Note that initial and

eventual reconstruction cannot be compared directly, as some events may have become fully reconstructed in the meantime and are thus no longer counted in the 3-elements-category, or subjects may have taken the element-combinations apart again and recombined them differently.

	Missing element				
3 elements remembered	**Object**	**Odour**	**Person**	**Place**	**Total**
Initially	0%	16.4%	0%	1.6%	18%
Eventually	1.7%	23.2%	3.2%	0.9%	29%

Table 8.9 Experiment 2, cued recall task: Percentage of events of which all elements but one are reconstructed correctly, by omitted element. Odour is most frequently omitted.

Events were retrieved via the following cues first: person 38%, object 18%, odour 7% place 5% (note that these percentages do not sum up to the total number of 66% 'initially remembered' because some events were retrieved by 2 cues simultaneously). Subjects thus show an overall cue preference in favour of the 'person' cue over the 'place'- and 'odour' cues in the cued recall setting, where the cues themselves do not have to be recalled from memory but are already present and merely have to be combined correctly.

Subjects did not seem to employ distinct strategies throughout. However, they often gave examples of well remembered associations, which hinted towards a facilitation for associations with a common *semantic* theme, that was either inherent, e.g. "chef" and "kitchen" or easy enough to be thought of e.g. "*cream*-coloured glove and smell of *coffee*-liquor". Note that all aspect-combinations per event and thus their semantic coherence varied between subjects.

Discussion

The cued recall experiment revealed clearly that subjects did not successfully retrieve complete events consisting of all four testable elements, neither at an initial retrieval attempt nor after the final retrieval attempt. On the other hand, the percentage of events for which more than 2 elements are correctly associated together increases from 25%

initially remembered to 48% eventually remembered. Subjects are thus often successful at re-attempting retrieval after a first attempt, and mostly add a third (and eventually fourth) element. This could reflect the use of (independent) pair-wise associations with either of the elements of the first pair.

In contrast to Experiment 1, that shared the virtual reality setting of Experiment 2 (but not the odour-element), performance in the 'object' condition was much higher than in the other (context-dependent) conditions of the recognition test. Possible explanations are that firstly, the total number of events was only 10 as compared to 20; secondly, the number of repeated exposures to objects in the recognition test was increased because of an additional 'odour' condition; and thirdly, that presentation of the odour distracted subjects from the other elements of context. These last two factors may have also contributed to the worse performance in the context-dependent question types in this experiment. Thus, in terms of the recognition memory performance, Experiment 2 rather compares to Spiers et al.'s (2001a) study, in which retrieval of different elements of an event was however found to be likewise independent.

Further, retrieval *independence* is complemented by retrieval *asymmetry*: The 'person' cue featured predominately as key element of an event by means of which other elements would be retrieved. 'Odour', by contrast, was most prominently forgotten and hardly served as a primary cue for the reconstruction of the event. Similarly, performance of the 'odour' cue in the forced-choice recognition test was worst. The success of a particular odour-cue stimulus was correlated with how nameable it was considered to be over all, thus indicating odour memory facilitation through available semantic information as has also been shown by Rabin and Cain (1984). However, this correlation was not found *within* subjects suggesting that performance was not necessarily influenced by a subject's (momentary) ability in naming the odour.

Chapter 8

General Discussion

A virtual reality paradigm was used to investigate how the context and content of a series of pseudo-realistic events were bound together in episodic memory. A paired forced choice recognition test probed retrieval of different aspects of these events (person, place, object, and in Experiment 2, odour). Retrieval performance was correlated between different contextual cues in order to test whether encoding of these events was dependent or independent. The findings are subsequently summarised:

Events are not encoded as holistic units

Subjects' retrieval success when cued with one element of an event did not correlate with retrieval success when cued with another element of that same event (Experiment 1). We thus conclude that events are not *encoded* holistically (at least in our virtual reality paradigm using pseudo-realistic events) since this would predict dependencies between the retrieval of the same event by different cues. By contrast, a model based on independent pair-wise associations between elements provides a good fit to the data. Results from an additional cued-recall test (Experiment 2), in which the subjects recombined all of the individual elements into the events that they had experienced, further suggests that recollection of events is rather partial and iterative in nature and not holistic. More information is added with each subsequent retrieval attempt. At the initial retrieval attempt only 7% of all events were retrieved fully, with 59% remembered partially and 33% not remembered at all. Importantly, this performance increases to 19% entirely remembered in the end as opposed to 62% partially remembered and 19% forgotten completely.

These results are inconsistent with the idea that episodic recollection corresponds to 're-experiencing' an event in such completeness and in such a realistic way that a mechanism of autonoetic awareness is required to disambiguate it from current perception, as seems to be suggested by Tulving (e.g. 2002). They are further inconsistent with the spirit of the 'locale-system' proposed by O'Keefe and Nadel (1978) in which an event is stored in a map-like set of relations, which were thought to

be egalitarian and not representing many different retrieval hierarchies and pair-wise encodings of single aspects.

Is it possible that the stimuli used somehow fail to capture the essence of autobiographical episodic information? For example, even though distinct contextual *elements* were used for each event in Experiment 1, all of the events still involved the same *action,* walking up to a person and "receiving" the object that appears as a result of that encounter. In Brewer and Dupree's (1983) study, different goal-directed actions, viewed on film, were remembered holistically. It may be that the similarity of the actions in our experiment caused interference between events that disrupted the holistic and distinct recollection of each one.

However, this interpretation is undermined by the similarity between these results and those in Wagenaar's (1986) study of his own autobiographical memory. Wagenaar found that some elements of an event formed better cues than others and also found that multiple cueing by different elements of an event increased the probability of retrieval in line with (and sometimes exceeding) the prediction of independent pair-wise associations. In addition, he reported many events that were only partially remembered, and a failure to retrieve around 20% of events (consistent with the final result in the cued recall of Experiment 2).

In line with Wagenaar (1986), the current findings also contrast with Jones' (1976) finding of independent but holistically encoded fragments. Or, put another way, there was only evidence for fragments including pairs of elements but not triples. As previously argued by Wagenaar (1986), some differences might be due to cue discriminability: In Jones' settings, subjects might easily learn that, within a list, each element of an event is unique and thus any fragment containing a given element will be specific to the single event containing that element. In autobiographical studies subjects would not in general be able to make that assumption, and in the virtual reality paradigm used in this study, cue complexity would make it harder to make such predictions.

In the case where a simple fragment model may not be sufficient to describe performance, other processes may become the performance-limiting factor. For instance, as Wichawut and Martin (1971) found, retrieval independence can be related to the strength of a formed association. They showed that after learning A-B and A-C associations, the responses B and C were retrieved independently so long as at least one of the pairs was well-stored in memory, but if both were weakly stored, retrieval dependencies arose.

Evidence for retrieval cue hierarchies

Different contextual cues were found to afford different levels of access to the memory of the content of the event (the object). This is consistent with Marr's (1971) model, the 'filing cabinet' model referred to by Wagenaar (1986) and the model of headed records (Morton et al., 1985; Morton & Bekerian, 1986), in which some elements of a memory are seen to be very efficient retrieval cues (e.g. the name of a person) but are much less easy to be retrieved themselves.

In the cued recall experiment, the 'person' cue was most frequently chosen to start retrieval of episodic information, contrasting with Jones' (1976) findings that cued recall probability was symmetric for either of two (perceptual) components of an event. As discussed above, the chances for subjects to evaluate cue-specificity over several trials were higher and the elements of context perhaps more similar and of reduced semantic complexity in Jones' experiments. Asch and Ebenholtz (1962) similarly demonstrated approximate symmetry in the recall of two-component visual patterns. They argued further that asymmetry in other circumstances could be due to differential availability of the components, perhaps due to differential levels of semantic association.

Clayton et al. (2001) suggested that 'where' was the predominant element binding an episode together in episodic-like memory in scrub jays compared to 'what' and 'when'. By contrast, retrieval performance of the 'place' cue was favoured neither in Experiment 1 nor Experiment 2. However, it is hypothesised that retrieval cue success (and preference) may depend on the circumstances: the crucial cue of retrieval might well shift away from 'place' to 'people', depending on the nature of information to be

remembered. Whereas for example for scrub jays caching food the most successful memory cues might well be places (triggering additional episodic information), for human subjects wandering around in (virtual reality) towns, the most relevant cues are more likely people who provide objects. The person might be given preference because she could hypothetically walk away and disrupt the 'where' whilst taking the 'what' away with her. Clayton et al.'s original paradigm (Clayton et al., 2001; Clayton & Dickinson, 1998) did not test memory for 'who' was involved in a caching event (but see Emery & Clayton, 2001). An alternative explanation would be that cue preference is dependent on the distinctiveness of cues of the same category across events. If for example the places are very similar, other cues will contribute more to the distinctiveness of the event.

Role of semantics in episodic memory

Tulving and Markowitsch emphasised that "encoding of information into the episodic system depends critically on the semantic system" (Tulving & Markowitsch, 1998, p.200). Further, early experimental investigations of human memory (e.g. Deese, 1959; Jenkins & Russell, 1952) and recent studies in people with dementia (Rusted et al., 2000) demonstrated that semantic relations play an important role in binding of episodic memory. If we understand "semantic relations" as a "knowledge-network" into which new episodic information can be integrated, then the following observations can be made on the role of semantic relations in our experiment: Partly, semantic relations were undermined in our study in which episodes consisted of random semantic consistency. There were only a few combinations of places, people, objects and smells, created by chance, that were inherently consistent (imagine for example 'kitchen', 'chef', 'cup and saucer' and 'smell of peanut-butter' in Experiment 2). However, whenever subjects encountered any semantic consistency, they happily made use of it to encode the pseudo-realistic events in virtual reality. This they reported in the post-experimental assessment of strategies used. Another finding suggests a significant role of semantic encoding for the olfactory context: Odorants which were more easily and more consistently given a label (in a perceptual test before the experiment), proved to be better retrieval cues compared to inconsistently labelled odours. This is in line with the report of Rabin and Cain (1984) that subjects remember the previous occurrence of

odours that they have labelled veridically at inspection better than odours they have labelled non-veridically. It is further evidence for odour traces in memory being less distinctive.

Olfactory cues are not especially evocative

The success of olfactory cues to retrieve episodes was relatively small compared to the other cues 'place' and 'person'. This was true even for semantically well-encoded odours and despite the use of generally familiar, distinct and easily identifiable odours (as evaluated in prior pilot experiments). Taking into account that perceptual features might account for this, and admitting that there is no information available about the extent to which the cues were matched semantically and perceptually across modality, another potential explanation is suggested nonetheless: As discussed in the Introduction to Part II (Chapter 7), olfactory stimuli are generally not tagged with a label easily, even if perceived familiar and even though they might have been labelled correctly just some minutes ago (e.g. Cain & Potts, 1996; Engen & Ross, 1973). The binding of label and olfactory percept is volatile. Thus, on the one hand, semantic integration of an odour enhances its success as a retrieval cue, as reported above and as shown previously (Lawless & Engen, 1977; Lyman & McDaniel, 1990; Rabin & Cain, 1984). But on the other hand an olfactory cue's frequent temporary failure to elicit a label might result in it being preserved in memory as a rather isolated and inaccessible trace. As such it might be a poor contextual cue, although by being recalled relatively rarely it might also remain a highly distinct cue. Corroborating this 'rarity-argument', there is indeed experimental evidence showing reduced retroactive interference in olfactory memory compared to other modalities (see Lawless & Engen, 1977; Rubin et al., 1984).

Conclusion

In a chain of pseudo-realistic events that consist of the same element-categories throughout, each event appears to be encoded in terms of *independent* pair-wise associations between its elements. If confirmed in other paradigms, this finding would argue against the idea that whole events are the units of episodic memory and are necessarily re-experienced in all their detail at retrieval.

It has been shown previously that the context-dependent retrieval of event aspects in this virtual reality paradigm is hippocampal-dependent (King et al., 2004). Thus, such results further question, whether episodic memory is organised in a map-like manner in the hippocampus with associations in which all elements can contribute equally. It seems to be possible that elements of an event can be retrieved individually and in various combinations. Further, in an experiment of cued recollection (see Experiment 2), we found that the event's content was retrieved most favourably via the 'person' cue as opposed to the 'place', 'object' or 'odour' cues. In that experiment, we found that olfactory information is less closely tied to the event and serves as a less potent retrieval cue than the other elements of our events. This might be linked to poor semantic representation of olfactory information.

In summary, hippocampal-dependent memory for events and their context is not necessarily holistic. In the experiments presented here the various elements comprising each memory appeared to be independently associated with each other. If more holistic encoding is possible, it is not triggered by the circumstances of the virtual context-memory paradigm presented here.

Chapter 9) The role of personal relevance in episodic memory: fMRI of memory cued by personally known, famous and unknown faces

Introduction

This study sought to investigate the role of the hippocampus in memory for stimuli with personal relevance as compared to memory for stimuli associated with general knowledge or novel stimuli. Moreover, we were also interested in the effect of personal relevance on stimulus-recognition. As discussed in the Introduction to Part II (Chapter 7), it has been argued that personal relevance is one important aspect in which autobiographical memories differ from episodic memory for laboratory-based stimuli (Maguire, 2001a). A number of recent studies have investigated people's real-world autobiographical memories (Addis et al., 2004; Cabeza et al., 2004; Gilboa et al., 2004; Maguire, 2001a) and consistently found hippocampal activation, unlike many earlier neuroimaging studies of episodic memory using laboratory-based stimuli (Shallice et al., 1994; Tulving et al., 1994b, but see King et al., in press). The method chosen to trigger real-world autobiographical memories in the experiment reported here was to use photographs of faces of the participants' friends. This has the advantage that participants don't have to be interviewed prior to testing, during which their memories would be re-encoded. Further, faces might be very strong retrieval cues and for this reason, recognition and identification of famous faces has been used to study the neural regions critical for long-term memory retrieval in the clinical context (e.g. Warrington & James, 1967).

The neural bases of face perception and identification have been well studied. It has been found that perceptual aspects of face processing primarily engage right occipital regions while face identification engages more anterior right ventral occipitotemporal regions, principally the midfusiform and parahippocampal gyri (Sergent et al., 1992). Bruce & Young (1986) proposed a model for face processing and recognition according to which at least two processing routes within the temporal lobe diverge after an initial stage of structural encoding: The dorsal visual stream provides perceptual analysis of

faces such as detecting age, race, gender and facial expression. The ventral pathway, the 'recognition route', contains 'face recognition units' including perceptual representations of familiar faces, and 'personal identity nodes'. 'Face recognition units' are required for subsequent retrieval of semantic information about the corresponding person. The model is consistent with the finding of neurons sensitive to face identity in the inferior temporal gyrus of the macaque monkey, compared to neurons in the superior temporal sulcus more sensitive to facial expression (Hasselmo et al., 1989). In an fMRI study, Haxby et al. (2000) also associated the lateral midfusiform area with processing of the invariant aspects of faces, corresponding to the recognition route of Bruce and Young (1986). However, the lateral midfusiform cortex might not be exclusively specific to faces, although it has been found to be generally activated during face perception, and moreover it is activated when perception of face stimuli is directly contrasted with non-face stimuli (Kanwisher et al., 1997). Further, while prosopagnosia (impaired face recognition) is most frequently associated with bilateral lesions to the occipitotemporal cortex (Damasio et al., 1982), right hemisphere damage has been shown to be sufficient to produce the deficit (De Renzi et al., 1994). In line with this, Warrington et al. (1984) found that semantic dementia patients with bilateral or primarily right-sided temporal lobe atrophy were impaired at recognising famous faces, while patients with predominantly left-sided temporal lobe atrophy were found to perform normally.

It has been argued that the additional naming of the faces, thus the retrieval of explicit semantic information, involves the temporal lobes *bilaterally* (Damasio et al., 1996). A study by Simons et al. (Simons et al., 2001, experiment 2) corroborates this notion: Two patients with semantic dementia affecting predominantly the left temporal lobe, showed good episodic memory for the previous presentation of faces of famous people when identical photographs of the celebrities were used at study and test, regardless of whether the patients could produce semantic information about them. When different photographs were used, the patients were still able to detect the famous faces seen previously if they retained a significant degree of semantic knowledge about them. However, their episodic memory for the previous presentation of famous faces about

whom they showed no evidence of knowledge was markedly impaired when different photographs were used in the study and test phases. Thus, when semantic information for the faces was lost (due to damage to the left temporal lobe) recognition was relying exclusively on perceptual features of the faces, presumably stored on the right.

A recent fMRI experiment by Henson et al. (2003) provided further evidence for this functional segregation of different levels of face processing in healthy human subjects: The contrast between familiar (famous) and unfamiliar faces was associated with activation in the *left* lateral midfusiform gyrus and *left* superior temporal lobe (as well as left medial superior frontal and bilateral orbitofrontal gyrus). By contrast, face perception (operationalised by the contrast of unfamiliar faces versus scrambled faces) was associated with *bilateral* lateral midfusiform and *right* superior temporal sulcus activation and activation decrease in medial occipital regions. Thus, face familiarity increased the haemodynamic response in the left lateral midfusiform cortex, possibly activating pre-existing perceptual representations, 'face recognition units' in the Bruce & Young (1986) terminology. The left temporal pole activations to familiar faces are interpreted to reflect retrieval of semantic information, perhaps via access to 'personal identity nodes'. Note that in Henson et al.'s (2003) study, the task was for participants to rate face symmetry, thus the face recognition was implicit. Another study, contrasting the identification of famous faces compared to recently encoded unknown faces (Leveroni et al., 2000), found a slightly different temporal lobe activation network, namely bilateral middle temporal lobe activation, left hippocampal, right parahippocampal and fusiform activation. Thus, famous faces for which 'personal identity nodes' exist, activated not only lateral temporal regions but also the hippocampus, perhaps suggestive of more episodic-like memory retrieval. Further, right lateralised posterior temporal activation was found for famous compared to recently encoded unknown faces. The interpretation of this includes the possibility that famous faces might be stored in a view-independent manner as compared to unknown faces. Alternatively, these areas could process perceptual novelty of the famous faces compared to the previously seen unknown faces.

In our study, we included famous faces, as well as participants' friends' faces and to unknown faces. We chose two subject populations; individuals who knew members of their own population but did not know members of the other population. Photographs of their friends were used to probe autobiographical memory. Thereby, each group's friends' photographs served as control photographs of strangers' faces to the other group in a balanced design (each face appearing equally in the 'familiar' and 'unknown' conditions across subjects). Thus we were able to further investigate Leveroni's (2000) finding of hippocampal activation, and to directly compare identification of personally known and famous faces. The inclusion of the third category, the famous faces, was also inspired by findings of Maguire and colleagues (Maguire et al., 2000; Maguire et al., 2001a; 2001b; Maguire & Mummery, 1999) who compared personal and public event memories and overall found left hippocampus and medial prefrontal cortex (BA10) to selectively support the retrieval of *personal* event memories. Thus, additionally to investigating the neural basis of autobiographical memory retrieval, we also compared retrieval of personally relevant information with more public information.

Finally, the basic task in which these stimuli were used (Phase 2) was recognition of prior presentation. A previous study (Henson et al. 2003) found that the type of stimulus (famous versus novel faces) modulates the activation corresponding to recognition of prior presentation. One aim of our study was to investigate the modulation caused by autobiographical stimuli. Thus, all three face types were presented twice: In Phase 1 participants were asked to identify a face as personally known, famous or unknown. In Phase 2 they performed a recognition test on the stimuli of Phase 1 regardless of face category.

Materials and Methods

Participants

14 right-handed volunteers, aged between 20 and 23, were recruited. They had no history of neurological illness and either had good eyesight or wore corrective contact lenses. They were part of either group A 'Ameela's friends' (5 female, 2 male) or B 'Jack's friends' (1 female, 6 male). Criterion for participation in the study was that

subjects of each group were to know personally a proportion of the faces presented as stimuli (see below). Written consent was obtained in accord with the Institute of Neurology ethics committee.

Stimuli

144 face images were prepared, belonging to one of three categories: famous faces, faces personally known to volunteer group A, and faces personally known to volunteer group B. Thus, on presentation of the whole range of stimuli, each group of subjects viewed faces a third of which were famous (*f*), one third personally known (*p*) and one third unknown (*u*) to them. Half of each category's images were of females and half of males. 'Ameela's friends' faces were taken from the UCL Medical School yearbook 2001 in electronic format, 'Jack's friends' faces were chosen from Jack's private collection of photographs. Images of contemporary famous people's faces were obtained from the Internet. We attempted to approximately match the famous faces to the other categories in depth and duration known as well as surface quality (neutral face

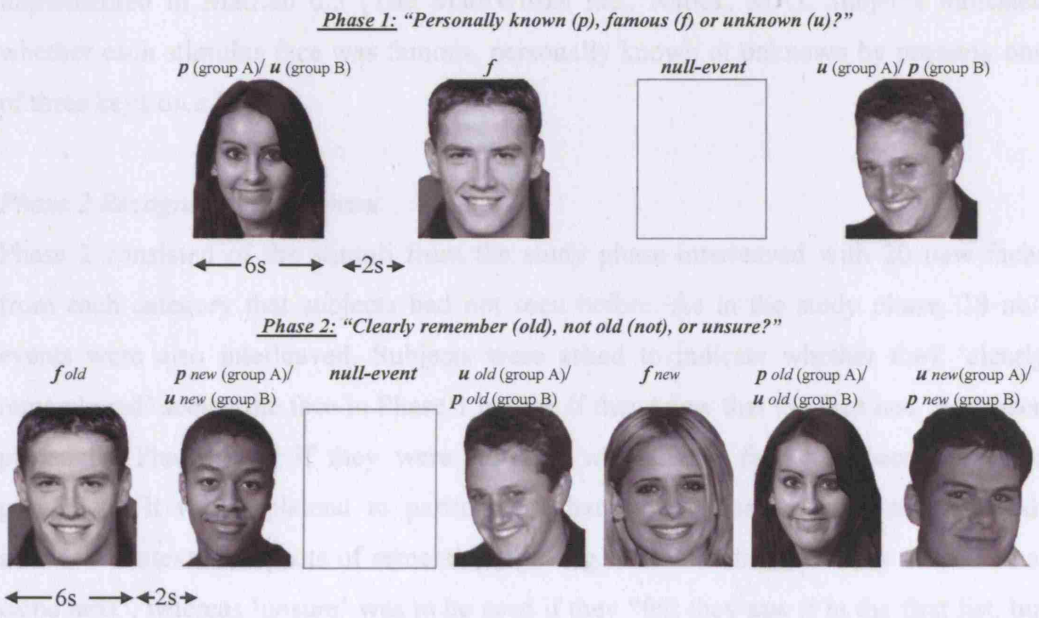


Figure 9.1 Illustration of experimental design. Phase 1: Subjects judged the face category; famous (f), personally known (p) or unknown (u). Phase 2: Faces from Phase 1 ('old'), and 'new' faces were presented. Subjects responded whether they 'clearly remembered' seeing the face in Phase 1 before, if they knew that the face had 'not' been present in Phase 1, or if they were 'unsure' whether the face had been presented previously.

expression, hairstyle, make up, etc.). Additionally, all faces were standardised into black and white pictures on a white background, see Fig. 9.1.

Pre-scan Training

Immediately prior to scanning, subjects undertook a shortened practice trial of the task they would do in the scanner, presented on a laptop computer. Subjects responded by pressing three keys simulating the keypad used in the scanner. The 18 stimuli used for practice were extra faces that were not subsequently presented in either phase of the actual task.

Scanning Experiment

Phase 1 "Friend, famous or unknown?"

Phase 1 involved the sequential visual presentation of 84 faces (consisting of 28 famous, 28 personally known to group A and 28 personally known to group B), plus 28 null events (presentation of a blank screen). Stimuli were presented using the Cogent 2000 software suite (Wellcome Department of Imaging Neuroscience, London, UK), as implemented in MatLab 6.5 (The MathWorks Inc., Natick, MA). Subjects indicated whether each stimulus face was famous, personally known or unknown by pressing one of three keys on a keypad.

Phase 2 Recognition experiment

Phase 2 consisted of the stimuli from the study phase interleaved with 20 new faces from each category that subjects had not seen before. As in the study phase, 28 null events were also interleaved. Subjects were asked to indicate whether they 'clearly remembered' seeing the face in Phase 1 before, if they knew that the face had 'not' been present in Phase 1, or if they were 'unsure' whether the face had been presented previously. It was explained to participants that the category 'clearly remembered' included contextual aspects of remembering, "e.g. remembering how they felt or what came next", whereas 'unsure' was to be used if they "felt they saw it in the first list, but without the above clarity and detail". The option 'unsure' was included in order to filter out episodic recollection from 'feeling of familiarity' and guessing. Subjects were instructed to respond as accurately and quickly as possible. Subjects indicated a

response by pressing one of three keys with their right hand. Response times were recorded.

Stimuli were projected onto a screen which the subjects viewed by means of a mirror above their eyes in the scanner. Presentation of faces was pseudo-randomised in both phases of the experiment. Care was taken that faces from the same category did not occur more than three times in a sequence. Each stimulus was presented for 6 seconds followed by a 2 second interval (a blank screen).

Post-scan Questionnaire

Following scanning, subjects completed a questionnaire about all 144 faces seen in the experiment. They assigned each face a category (famous, personally known or unknown) and rated it for attractiveness (on a scale from 1 to 6). For the personally known and famous faces, they additionally answered

- How long they had known the person (duration known), in years
- How well they knew the person (from 1 to 6)
- How strong an emotional response they felt for the person (1 to 6, positive, negative or other)

fMRI scanning

40 T2*-weighted axial echoplanar images (EPI) per volume (3x3x3mm voxels; T_E = 65ms) with blood oxygenation level dependent (BOLD) contrast were acquired using a 3 Tesla Siemens VISION scanner (Siemens, Erlangen, Germany). EPIs consisted of 2mm thick axial slices (spacing = 1mm), acquired in descending order. A total of 570 volumes were collected continuously with an effective repetition time (TR) of 2.6s, with the first 5 volumes in each session being discarded to allow for T1 equilibration effects. T1-weighted structural images were additionally obtained after completion of the task (1.5x1.5x1.5 mm voxels, 3d acquisition).

Data analysis

Data were analysed using Statistical Parametric Mapping (SPM_devel, April 2004, Wellcome Department of Cognitive Neurology, UK). The T2-images were unwarped, then spatially normalised to a standardised echo-planar image (EPI) template and

smoothed (with an 8mm Gaussian kernel). The structural images were coregistered with the mean unwarped functional image and then normalised using the same parameters.
For each subject, the fMRI time-series was high-pass filtered (minimum cut-off period 128s), and modelled as the weighted sum of regressors corresponding to effects of interest. The conditions of interest were (labelled in terms of the response-type and stimulus-type pair): for Phase 1 'personally known' (p), 'famous' (f) and 'unknown' (u), for Phase 2 'remembered old' (recollection-hits), 'unsure old' (guessed-hits), 'not old' (forgotten/ misses), 'not new' (correct rejections), and a combined regressor for 'remembered new and guessed new' (false alarms). In addition, a regressor relating to the null-event was included. The regressors were defined as a series of stick-functions timed at 500ms after the appearance of the test pictures on the screen. The timings were derived from logs produced by the Cogent display program. The regressors were convolved with the haemodynamic response function (HRF) and the parameters for the best fitting model were estimated by SPM. On the basis of these parameter estimates the following second level analyses were performed:

A one way within subjects ANOVA on face type using the parameter estimates for the regressors from **Phase 1 ,**

For **Phase 2** a 3x2 repeated measures ANOVA over ***face types x recollection hits/correct rejections***. We were interested in the interaction effect and in the main effect of face type (pooled over hits/correct rejections).

Parametric modulation: An additional model was generated for Phase 1, including the above regressors for face type 'famous' and 'personally known' modulated by the parameter 'duration known' ("How long do you know this person?"), and all three regressors 'famous' and 'personally known' and 'unknown' modulated by the parameter 'attractiveness'. The parameters were taken from the post-scanning questionnaire. In this analysis, at the second level single t-tests were run on the subjects' parameter estimates for each parametrically modulated regressor revealing areas with an increase or decrease in activation according to the length of time each type of face had been known and how attractive it was rated.

All results are reported at FDR[9.1] = 0.05, minimum cluster size kE =10 voxels, unless otherwise specified.

Results

Behavioural results

Performance and reaction times:

In the Phase 1 face categorisation task, 94.1% of famous faces were correctly categorised, 88% of personally known faces, and 99.2% of unknown faces. Subsequent imaging analyses of Phase 1 include only correctly categorised faces in the 'famous' or 'personally known' regressors, the 'unknown' regressors included all faces categorised as unknown. For Phase 2 participants' face categories were taken from the questionnaire ratings. Subjects show a reaction time effect of face type in Phase 1 ($F_{2,22}$=5.87, p<0.01), see Fig. 9.2. Single paired comparisons reveal that subjects responded fastest to famous as opposed to personally known and unknown faces (repeated measures t-tests, p<0.05 and p<0.001 respectively), but there is no difference

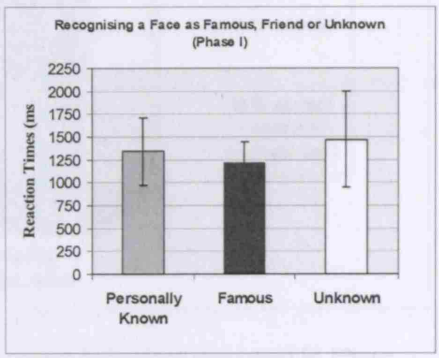


Figure 9.2 Phase 1: Reaction times as subjects responded whether the face was *personally known*, *famous*, or *unknown*.

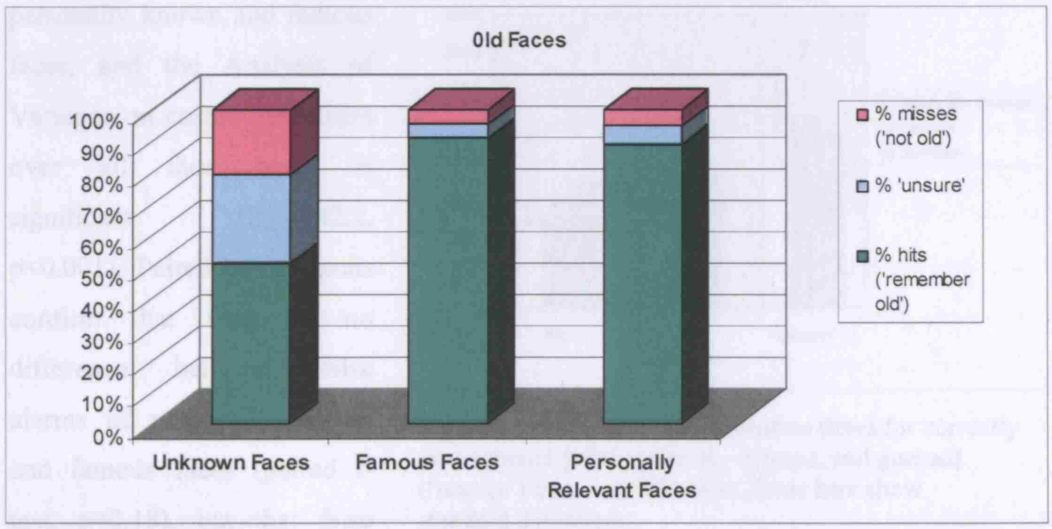


Figure 9.3 Phase 2: Percentage of answers given for "old" faces (presented in Phase 1), per face type.

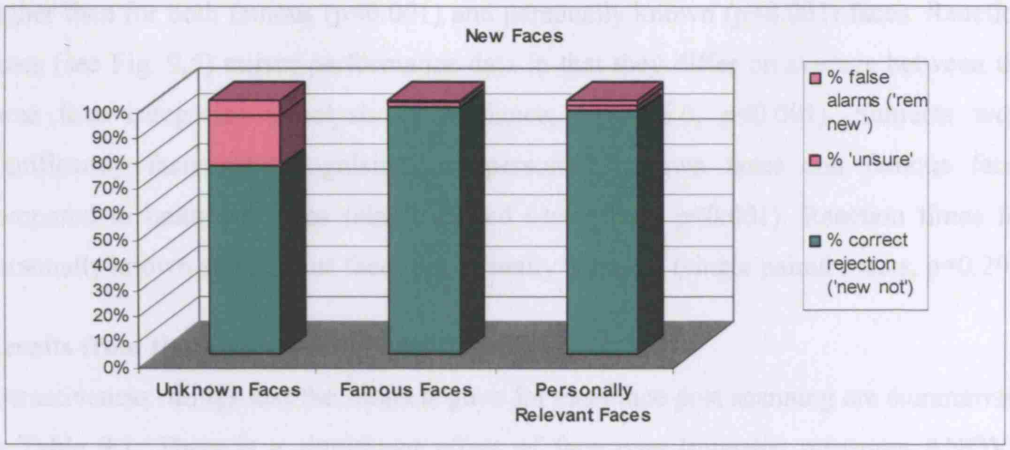


Figure 9.4 Phase 2: Percentage of answers given for "new" faces (not presented in Phase 1), per face type.

between personally known and unknown faces (p=0.13). The distribution of answers for faces judged as old in Phase 2 is shown in Fig. 9.3.

Analysis of Variance reveals a significant effect of face type ($F_{2,26}$=76.6, p<0.001). Subsequent paired t-tests on hits over all face types show that previous presentation of unknown faces is remembered less well compared to personally known (p<0.001) and famous (p<0.001) faces, but there is no difference between personally known and famous faces (p=0.35). Fig. 9.4 shows a similar trend for unknown faces to yield more false alarms than the personally known and famous faces, and the Analysis of Variance on correct rejections over all face types is significant ($F_{2,26}$=42.2, p<0.001). Paired comparisons confirm that there is no difference between false alarms of personally known and famous faces (paired t-test, p=0.18), but that false alarms for unknown faces are

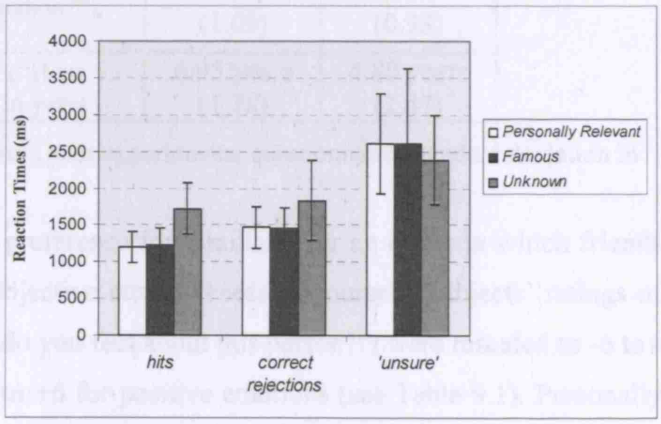


Figure 9.5 Phase 2: Average reaction times for correctly remembered (hits), correctly rejected, and guessed ('unsure') items per face type. Error bars show standard deviations.

higher than for both famous ($p<0.001$) and personally known ($p<0.001$) faces. Reaction times (see Fig. 9.5) mirror performance data in that they differ on average between the three face categories (Analysis of Variance, $F_{2,22}=36.0$, $p<0.001$). Subjects were significantly faster at recognising old personally known faces and famous faces compared to unknown faces (single paired t-tests both $p<0.001$). Reaction times for personally known and famous faces are virtually identical (single paired t-tests, $p=0.29$).

Results from the post-scanning questionnaire

Attractiveness ratings that the subjects gave for each face post scanning are summarised in Table 9.1. There is a significant effect of face type (repeated measures ANOVA $F_{2,26}=40.15$, $p<0.001$). Single comparisons reveal that famous faces are rated significantly more attractive than personally known and unknown faces (both $p< 0.001$), and that personally known faces are rated more attractive than unknown faces ($p=0.001$) (note that the faces were counterbalanced across personally known and unknown face

	Face Category		
	Famous	***Personally known***	***Unknown***
Mean *attractiveness* ratings, scale = 1 to 6	3.73 (1.01)	3.06 (0.79)	2.24 (0.76)
Mean ratings of '*emotionality*' ("How emotional do you feel about this person?"), scale = -6 to +6	1.69 (1.03)	2.35 (0.98)	
Mean ratings of '*duration known*' ("How long do you know this person?"), in years	6.95 years (1.78)	4.80 years (2.47)	

Table 9.1 Subjects' faces ratings from post-experimental questionnaire (standard deviation in brackets).

categories). This could reflect a preference for familiarity or an effect in which friends are partially selected by their subjective attractiveness to yourself. Subjects' ratings of '*emotionality*' ("How emotional do you feel about this person?") were rescaled to -6 to -1 for negative emotions and +1 to +6 for positive emotions (see Table 9.1). Personally known faces are rated as more emotionally salient than famous faces (t-test, $p=0.018$) but both face types are rated rather neutrally. Finally, the duration known for personally known faces is shorter than for famous faces (t-test, $p=0.010$), and more variable, see Table 9.1.

fMRI results

First I will report the findings from Phase 1, the ANOVA on face type (a), and the separate model investigating parametric modulation (b). Subsequently I will turn to the findings from Phase 2, the recognition experiment, reporting main effect of face type (pooled over hits/correct rejections) and the interaction effect.

area			x,y,z (mm) of cluster-peak:	T-value	k_E
L	Anterior Ventromedial Prefrontal Cortex	BA 11	-9 45 -12	6.22	4.82
R	Anterior Dorsomedial Prefrontal Cortex, ext. contralat.	BA 9	9 54 21	5.52	4.45

Table 9.2 Significant activation peaks in the contrast '**P>F**' of Phase 1, "recognising a face as a friend vs. recognising a famous face" (Height threshold T=4.49, FDR=0.05, extend threshold k_E = 10 voxels).

a. Phase 1, effect of face type

Two hypothesis-driven second level contrasts were computed for Phase 1: **P>F** (and the inverse, F>P); recognising a friend as a friend compared to recognising a famous person as a famous person; **(P+F)>U** (and the inverse, U>(P+F)); recognising a face (either as famous or as a friend) compared to looking at an unfamiliar face. **P>F** showed two anterior medial prefrontal peaks (BA10), see Fig. 9.6 and Table 9.2.

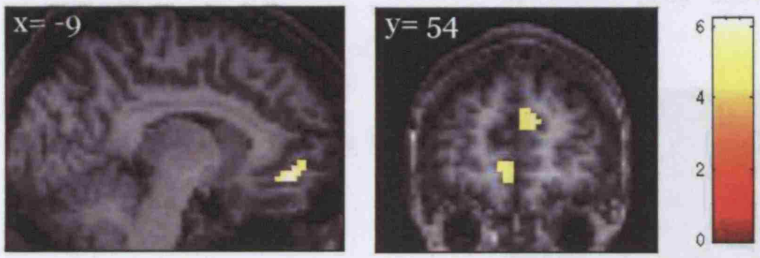


Figure 9.6 Contrast '**P>F**' of Phase 1 "recognising a face as a friend vs. recognising a famous face", rendered on a normalised structural scan of one subject. Anterior prefrontal activation.

The contrast **F>P** revealed no activation peak at the threshold FDR=0.05, k_E =10. In the contrast **(P+F)>U**, interestingly, the strongest activation peak is situated in the anterior prefrontal cortex (BA 11/10), as in P>F, extending into the hypothalamus on the left, see Fig. 9.7 and Table 9.3. Further, there is strong bilateral hippocampal activation, extending to the parahippocampal gyrus on the right, see Fig. 9.8. Smaller peaks include the right temporal pole and posterior cingulate. Percent signal change analyses for the

area			x,y,z (mm) of cluster-peak:	T-value	k_E
L	Medial Frontal Gyrus	BA 11	-9 45 -12	6.55	462
R	Hypothalamus		6 0 -9	5.76	subpeak
bilat.	Hippocampus, extending to Parahippocampal Gyrus on the right		24 -18 -24	5.54	121
			27 -30 -18	5.19	subpeak
			-30 -21 -21	4.6	28
R	Temporal Pole	BA 21	57 6 -27	4.84	52
bilat.	Posterior Cingulate	BA 31 / 23	9 -60 21	3.88	12
			-3 -60 18	3.75	subpeak

Table 9.3 Significant activation peaks in the contrast '**(P+F)>U**' of Phase 1, "recognising a face vs. looking at a stranger's face" (Height threshold T=3.66, FDR=0.05, extend threshold k_E = 10 voxels).

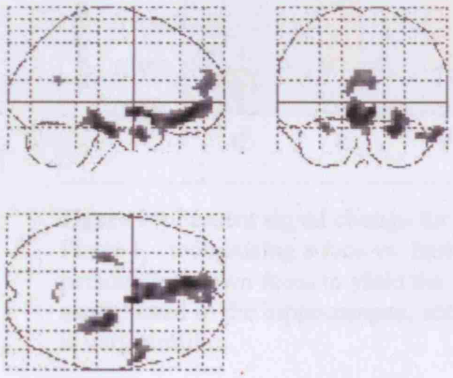


Figure 9.7 Contrast '**(P+F)>U**' of Phase 1, "recognising a face vs. looking at a stranger's face". Glassbrain-view. For details see Table 9.3.

different responses in the (P+F)>U contrast reveal a trend for greater activation for personally known faces than famous faces, see Fig. 9.9. However, generally, and especially in the hippocampus, activation for famous and personally known faces is very similar. For the contrast **U> (P+F)**, no activation peak showed at FDR=0.05, k_E =10.

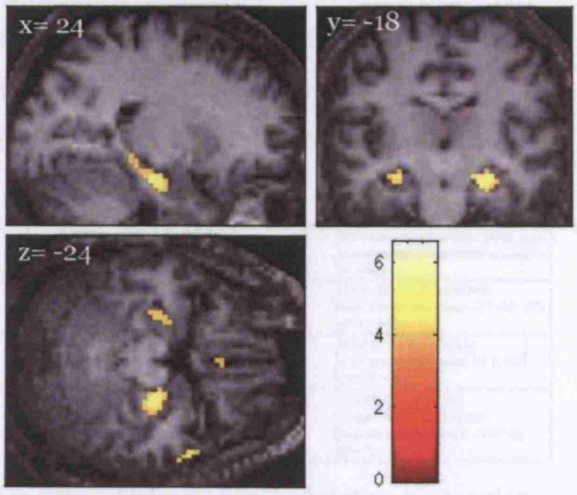


Figure 9.8 Contrast '**(P+F)>U**' of Phase 1, "recognising a face vs. looking at a stranger's face". Rendered on one subject's normalised structural scan. Bilateral hippocampal activation.

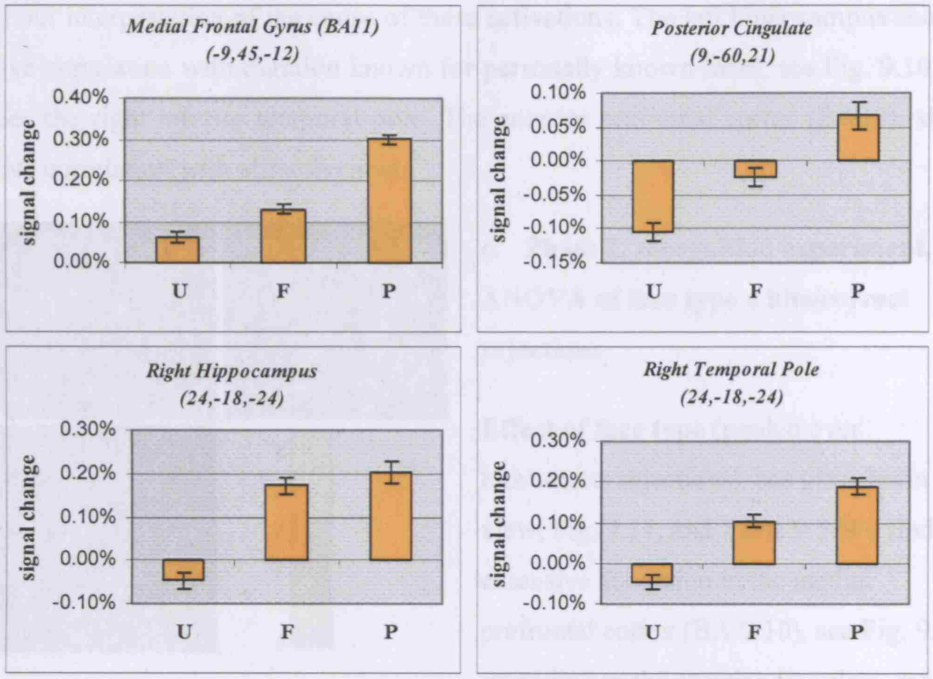


Figure 9.9 Percent signal change for voxels of interest in the contrast '**(P+F)>U**' of Phase 1, "recognising a face vs. looking at a stranger's face". There is a trend for personally known faces to yield the strongest signal change. However, and this is accentuated in the hippocampus, activation for famous and personally known faces is very similar.

b. Phase 1: Parametric modulation analyses

Areas showing an effect of parametric modulation are reported if they fall within the areas found to be activated in the basic comparisons reported above, at the lowered threshold of $p<0.001$ uncorrected, ($k_E=10$), see Table 9.4. The aim of these analyses is

contrast	positive correlation with	area			x,y,z (mm) of cluster-peak:	T-value	k_E	referring to activation peak (x,y,z in mm) in other contrast (contrast in brackets)
P	durkn	L	Hippocampus		-30 -12 -33	5.52	16	near -30 -21 -21 (nearest suprathreshold voxel: -27 -12 -27) ((P+F)>U)
		R	Temporal Pole	BA 21	45 0 -42	5.53	21	near 57 6 -27 (nearest suprathreshold voxel: 51 6 -33) ((P+F)>U)
	attract	L	Medial Frontal Gyrus	BA 10	-6 60 -3	4.44	19	• -9 45 -12 ((P+F)>U • near -9 45 -12 (nearest suprathreshold voxel: -6 57 -3) (P>F)

Table 9.4 Phase 1: Significant activation peaks for effect of **parametric modulation** by duration known ('durkn') or rated attractiveness ('attract') (Height thresholds T=3.93 (durkn), T=3.85 (attract), $p<0.001$ uncorr., extend threshold $k_E = 10$). At this lowered threshold, only activations are reported that also occur in main contrasts of Phase 1, see last column.

to aid our interpretation of the cause of these activations. The left hippocampus shows a positive correlation with duration known for personally known faces, see Fig. 9.10, and so does the right inferior temporal pole. The anterior prefrontal cortex (BA10), shows positive correlation with attractiveness.

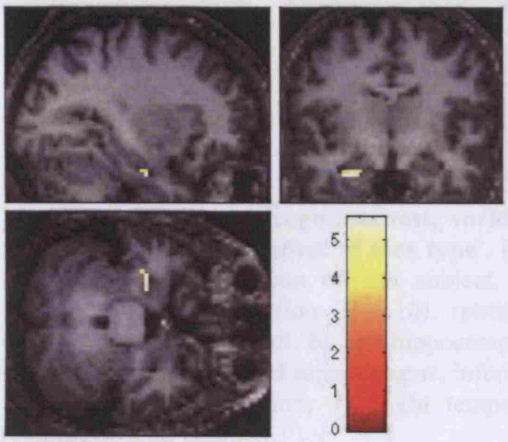


Figure 9.10 Effect of **parametric modulation** with '**duration known**'(Phase 1). Rendered on one subject's normalised structural scan. Left hippocampal activation.

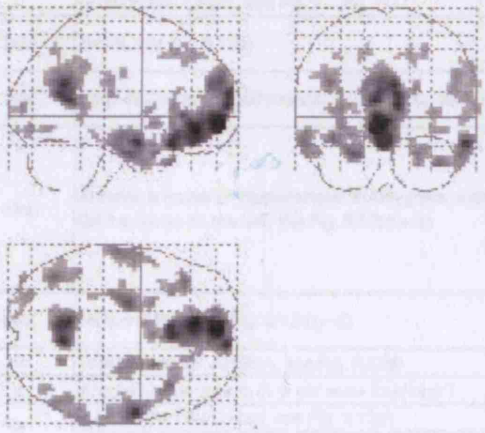


Figure 9.11 Phase 2, recognition test, 'effect of face type', see Table 9.4. Glassbrain-view.

c. Phase 2, recognition experiment, 3x2 ANOVA of face type x hits/correct rejections

Effect of face type (pooled over hits/correct rejections), see glass brain view, Fig. 9.11, and Table 9.5:We find extensive activation in the medial prefrontal cortex (BA 9/10), see Fig. 9.12a, extending to the anterior cingulate, more prefrontal activation on both sides dorsolaterally (BA8/6) and orbitofrontally (BA47) on the left. Activation peaks in the medial temporal lobes include anterior and posterior hippocampus and amygdala, bilaterally, see Fig. 9.12b and c, and in the lateral temporal lobes bilateral temporal pole (BA38, extending to BA 20/21), see Fig. 9.12c and d. A view at the right lateral surface, see Fig. 9.12d, further reveals three parietal peaks, in the temporoparietal junction (BA39) and in the inferior parietal lobule (BA40). Posterior, parietal and occipital activation include the left angular gyrus (BA39/40), bilateral retrosplenium, see Fig. 9.12a, left inferior occipital, see Fig. 9.12b and bilateral middle occipital

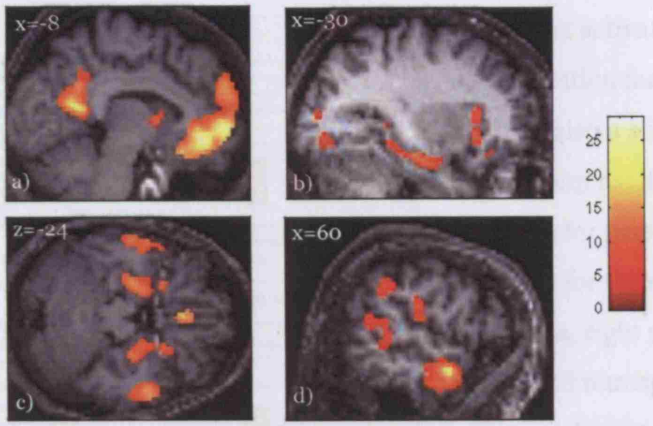


Figure 9.12 Phase 2, recognition test, various activation peaks showing in the 'effect of face type'. Rendered on a normalised structural scan of one subject. **a)** Extensive medial prefrontal activation (BA 10), retrosplenium, and head of caudate on the left. **b)** Left hippocampus and insula, **c)** Bilateral amygdala and hippocampus, inferior frontal and lateral temporal activation, **d)** Right temporal pole and temporoparietal junction.

cortex. Finally, bilateral head of caudate, see Fig. 9.12a, and insula, see Fig. 9.12b show significant activation. Zooming in on the percent signal change at these activation peaks, we find mainly two different patterns (see Fig. 9.13a-c compared to 9.13d&e): Firstly, for both, recognised old faces ('hits') and correctly rejected new faces, unknown faces (u)

area			x,y,z (mm) of cluster-peak:	F-value	k_E
Medial Frontal Gyrus, see Fig. 9.12a)		BA 10	-6 57 -3	28.48	1253
Anterior Cingulate		BA 25	0 9 -6	11.61	29
bilat.	Anteromediodorsal PFC, extending latero-posteriorly	BA 8/6	18 39 48	9.24	62
			-18 39 48	8.28	18
L	dorsolateral PFC		-39 15 45	7.99	10
L	Orbitofrontal Cortex, see Fig. 9.12c)	BA 47	-39 33 -15	14.46	36
bilat.	Insula, see Fig. 9.12b)		-33 21 -6	11.23	63
			36 24 3	9.98	41
bilat.	Head of Caudate (subthreshold on the right), see Fig. 9.12a)		-9 3 3	9.11	15
			6 3 3	8.15	9
bilat.	Anterior & Posterior Hippocampus & Amygdala, extending to Posterior Orbital Gyrus on the left, see Fig. 9.12b) + c)		-24 -9 -27	16.61	143
			-24 6 -21	11.01	subpeak
			-30 -33 -15	7.99	subpeak
			24 9 -27	13.56	128
			24 0 -33	10.77	subpeak
			27 -15 -24	10.67	subpeak
bilat.	Temporal Pole, see Fig. 9.12c) + d)	BA 38, ext. 20/21	60 -3 -18	21.74	265
			-60 -15 -15	13.04	171
R	Temporoparietal Junction, see Fig. 9.12d)	BA 39	51 -63 30	10.92	187
L	Angular Gyrus (peaks in *'p old rem> f old rem'*)	BA 39/40	-42 -66 27	14.06	142
R	Superior Parietal Cortex, see Fig. 9.12d)	BA 40	63 -42 39	9.61	34
	Inferior Parietal Lobule, see Fig. 9.12d)		63 -24 27	9.34	47
bilat.	Retrosplenium/ Precuneus, see Fig. 9.12a)	BA 30/31 & 7	-9 -54 12	21.74	418
			-15 -66 51	8.76	17
			21 -60 21	12.11	23
L	Inferior Occipital Gyrus	BA 18	-30 -84 -9	9.49	35
bilat.	Middle Occipital Gyrus	BA 19	-42 -90 6	9.46	33
			42 -72 -12	9.04	14

Table 9.5 Phase 2, recognition memory test: Significant activation cluster peaks in the **'effect of face type'** (Height threshold F=6.45, FDR<0.05, extend threshold k_E = 10 voxels).

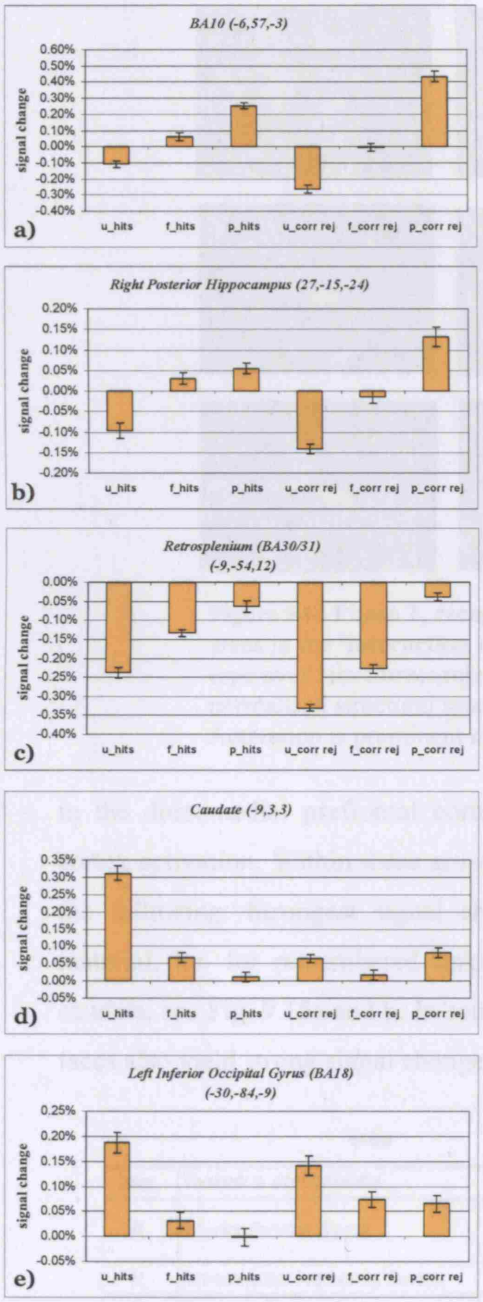


Figure 9.13 Phase 2, recognition memory test: Percent signal change for voxels of interest in the **effect of face type**. See text for a discussion of the apparent patterns.

show least activation and famous faces (f) show less activation than personally known (p) faces. There is also a slight habituation effect manifesting itself in less activation from new to old faces for personally known faces. This pattern is shown for the medial frontal lobe (BA10), see Fig. 9.13a, right posterior hippocampus, see Fig. 9.13b, and retrosplenium, see Fig. 9.13c, and also occurs in the anterior cingulate, bilateral anterior and posterior hippocampus, bilateral dorsolateral prefrontal cortex (BA 8/6), left inferior frontal gyrus (BA 47), right temporoparietal junction, left angular gyrus, and bilateral temporal poles (BA 38). The second pattern shows strongest signal changes for recognised unknown faces. It is prominent in the head of the caudate, bilaterally, as shown in Fig. 9.13d, and in visual processing areas, i.e. bilateral middle occipital gyrus (not shown) and left inferior occipital gyrus, see Fig. 9.13e.

Interaction effect

The effect of interaction of face type and remember old/correctly rejected new only yields a weak signal (no significant peaks at FDR = 0.05). Areas active at $p<0.001$ uncorrected ($k_E = 10$) are reported, for which prior hypotheses exist, see Table 9.6. The strongest effect is seen in the thalamus and head of caudate bilaterally, see Fig. 9.14. There is also a group of right prefrontal peaks in the inferior frontal cortex (BA47/11) and

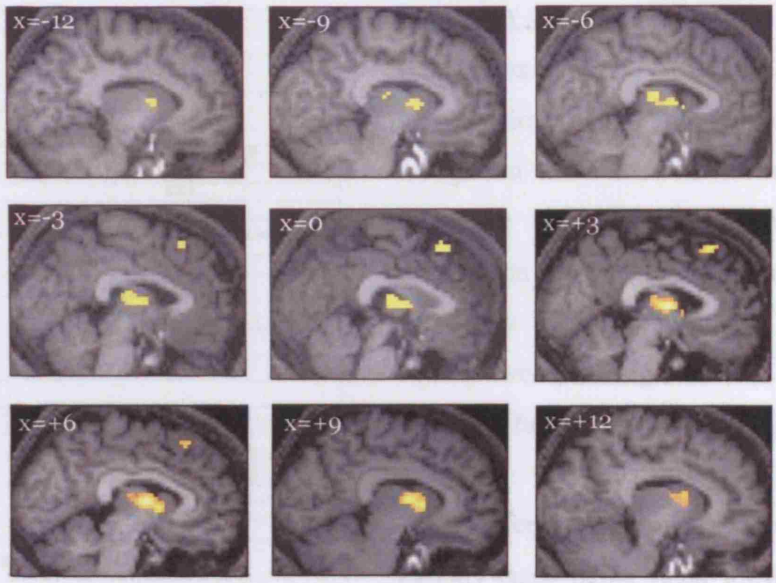


Figure 9.14 Phase 2, recognition memory test: Significantly active areas in the **'interaction effect'** (repeated measures ANOVA of face type over hits/correct rejections). Rendered on one subjects normalised structural scan. Sagittal slices from x=-12 to x=12. Activation is prominent mainly in the thalamus and head of caudate.

in the dorsomedial prefrontal cortex (BA8). Finally, we find right superior parietal cortex activation. Within these areas, the typical pattern driving the interaction effect is the following: Strongest signal changes occur for recognition of recently encoded material, i.e. for remembered unknown faces, most prominent in the thalamus and caudate, see Fig. 9.15a and b. In some areas, new/ correctly rejected (personally) known faces also yield strong signal changes, see Fig. 9.15a and c.

area			x,y,z (mm) of cluster-peak:	F-value	kE
bilat.	Thalamus and Caudate		6 -6 6	17.69	169
R	Inferior Frontal Gyrus	BA 47 & 11	27 21 -18	13.13	19
			36 36 -15	11.42	11
R	Dorsomedial Prefrontal Cortex	BA 8	3 27 54	10.96	25
R	Superior Parietal Cortex	BA 7	36 -75 48	9.31	10

Table 9.6 Phase 2, recognition memory test: Significant cluster peaks of the **'interaction effect'**. Height threshold F=7.70 (p=0.001 uncorr.), extend threshold k_E = 10 voxels.

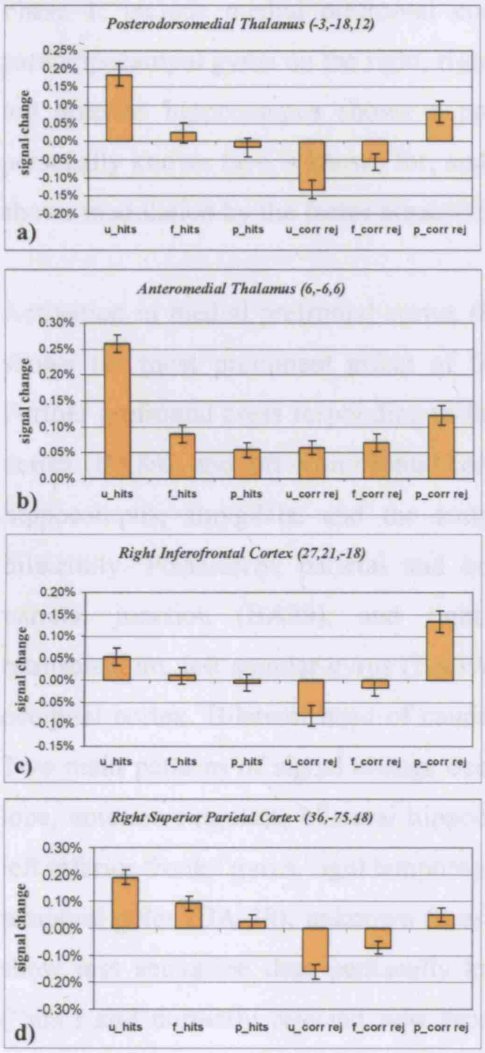


Figure 9.15 Phase 2, recognition memory test: Percent signal change for voxels of interest in the **'interaction effect'**. Signal change is highest for remembered unknown faces and for correctly rejected (personally) known faces.

Summary of results

Behavioural data (performance and reaction times) show that famous faces are recognised as famous faster than friend's faces are recognised as friends. In the recognition memory test famous and personally known faces are recognised equally well and significantly better than unknown faces.

Faces differ in rated attractiveness, with the famous faces being rated most attractive, but also with the personally known faces being rated more attractive than the unknown faces. Note that half of the participants' personally known faces were the other half of the participants' unknown faces, thus, faces of friends, beyond superficial attributes, are given higher attractiveness scores than strangers. Personally known faces were also rated as evoking stronger emotional responses than famous faces, and had been known for a shorter period of time.

Despite several attribute differences between the famous and personally known faces, the neural activation yielded by the two face categories overlap hugely. The only significant difference in recognising a personally known versus a famous face in Phase 1 was found in the anterior medial prefrontal cortex (BA10). Common areas of activation, as revealed by patterns of signal change in areas activated by the contrast (P+F)>U in

Phase 1, include medial prefrontal cortex, bilateral hippocampus, extending to the parahippocampal gyrus on the right, right temporal pole and the posterior cingulate. The left anterior hippocampus shows a positive correlation with the length of time a personally known face is known for, and so does the right inferior temporal pole. BA10 shows modulation by the factor attractiveness for personally known faces.

Activation in medial prefrontal cortex (BA 9/10), extending into the anterior cingulate shows the most prominent effect of face type (pooled over hits/correct rejections). Further prefrontal areas responding to face type include bilateral dorsolateral prefrontal cortex (BA8/6) and left orbitofrontal cortex (BA47). There is also a strong signal in the hippocampus, amygdala, and the temporal poles (BA38, extending to BA 20/21) bilaterally. Posteriorly, parietal and occipital activation include the right temporo-parietal junction (BA39), and right inferior parietal lobule (BA40), bilateral retrosplenium, left angular gyrus (BA39/40), left inferior occipital, and bilateral middle occipital cortex. Bilateral head of caudate and insula also show significant activation. Two main patterns of signal change occur in these areas: Firstly, in the medial frontal lobe, anterior cingulate, bilateral hippocampus, bilateral dorsolateral prefrontal cortex, left inferior frontal gyrus, right temporoparietal junction, left angular gyrus, and bilateral temporal poles (BA 38), unknown faces (u) show least activation and famous faces (f) show less activation than personally known faces (p) for both recognised old faces ('hits') and correctly rejected new faces. There is a slight tendency for habituation occurring from new to old faces, mainly for personally known faces. Secondly, another pattern is prominent in the head of the caudate, bilaterally, as well as in visual processing areas (bilateral middle occipital and left inferior occipital gyrus), where signal changes are strongest for recognised unknown faces.

A modest effect of interaction of face type *x* hits/correct rejections is shown in the thalamus and head of caudate, bilaterally. There are further peaks of activation in the right inferior frontal cortex (BA47/11), right dorsomedial prefrontal cortex (BA8), and right superior parietal cortex. The typical pattern of signal change in this interaction consists of strongest signal changes for recognition of recently encoded material on the

one hand, i.e. for remembered unknown faces, and correctly rejected (personally) known faces on the other hand.

Discussion

As a main finding we report that the hippocampus is involved in the recognition of a familiar face (personally known or famous), both in a task where subjects were told to identify a face as friend or famous (Phase 1), and in a task where subjects were instructed to recognise faces from a previous list of study faces (recognition paradigm, Phase 2). However we did not find significant hippocampal activation in the interaction between face type and hits/ correct rejections. Behaviourally, famous faces (f) are identified faster than personally known faces (p) and unknown faces (u) in Phase 1, whereas the only region to yield differential activation in the contrast between personally known faces and famous faces in Phase 1 is the medial prefrontal cortex (BA10). This region has been reported to be involved in self-relevant processing (e.g. Cabeza et al. 2004; Craik et al., 1999; Levine et al., 1998; Maguire, 2001a; Maguire et al., 2001b; Wicker et al., 2003, see Introduction to Part II, Chapter 7, for a review), also see below. The hippocampus by contrast is significantly activated in the contrast '(P+F)>U' in Phase 1 and in the effect of face type in Phase 2. Additionally, the left hippocampus shows signal modulation by how long a face is known, for personally known faces. Other areas involved in the recognition of a familiar face (personally known or famous) are congruent with the episodic memory retrieval network (e.g. Burgess et al., 2001b; King et al., 2005; see Maguire, 2001a for an overview) as described in the Introduction to Part II (Chapter 7). They include dorsolateral prefrontal cortex, medial prefrontal cortex, anterior cingulate, temporoparietal junction and retrosplenium. These results are discussed in greater detail and integrated with previous findings below.

Recognition facilitation for known material

From the literature on the self-reference effect (Rogers et al., 1977, in Craik et al., 1999), which states that stimuli in relation to the self are recognised better than stimuli with no specific relation, we might expect that autobiographical significance influences

episodic memory processes. Accordingly, Westmacott & Moscovitch (2003) have shown that participants recognised significantly more names judged to be autobiographically significant by a large group of age-matched peers. The authors argue that it may be easier to access or compute the representations of personally relevant semantic concepts because they include a rich network of contextual episodic associations that exist over and above abstract semantic features. Moreover, this personally relevant contextual episodic component is thought to be mediated by the hippocampus. Our results directly corroborate this hypothesis. There was a significant performance difference between familiar (personally known and famous) faces compared to unknown faces in the recognition test (Phase 2). This was accompanied by a significant effect of face type in areas associated with the episodic memory retrieval network including the hippocampus.

Another way of interpreting the difference between previously known and unknown faces in the '(P+F)>U' contrast of Phase 1, as well as the effect of face type and the interaction in the ANOVA of the recognition experiment (Phase 2), concerns view (in)dependence (Leveroni et al., 2000). It has been argued that the processing of unfamiliar faces relies on view-dependent representations, whereas familiar face recognition draws from view-independent representations based on multiple views of the same face (Treves & Rolls, 1992; Young et al., 1993, in Leveroni et al., 2000). Leveroni et al. (2000) found recognition of newly learned faces to produce significant activation in the right supramarginal gyrus. Our study yields activation in the right superior parietal cortex adjacent to the region found by Leveroni et al. (2000) in the interaction of face type *x* hits/correct rejections. Analyses of percent signal change for the interaction effect indeed point to the effect being driven by high activation for recognised newly learned faces (see Fig. 9.15d). This interpretation is congruent with the role this brain region takes in egocentric representations and translations between different egocentric and egocentric to allocentric representations in spatial memory (e.g. Andersen et al., 1985, 1993; Snyder et al., 1998, see Burgess et al., 2002) which was discussed in Part I (Chapter 2) and in the Introduction to Part II (Chapter 7).

Personal relevance: medial prefrontal, not hippocampal

Whereas there was a strong effect in the hippocampus and other areas related to the episodic memory retrieval network as an effect of face type in the recognition test (Phase 2), the signal change in the hippocampus was highly similar for both personally known and famous faces. The overall pattern was of less signal change the less known a face, the strongest for personally known and stronger for famous than unknown faces. However, personally known faces did not differ significantly from famous faces in terms of medial temporal lobe activation. The only area to yield a significant difference was the anterior medial prefrontal cortex (BA10), an area reportedly related to personal relevance or the representation of the 'self' (Cabeza et al., 2004; Craik et al., 1999; Maguire, 2001a). The interesting lack of significant differential activation between personally known and famous faces in other areas might be partially traced back to the selection of the two experimental groups and the choice of stimuli. The photographs of the participants' friends and fellow students do not necessarily represent their closest and autobiographically related friends, but rather some more cursory acquaintances. Moreover, famous faces largely consisted of contemporary faces that subjects would encounter regularly on TV, in newspaper, magazines, etc. (they were rated to be known for about 7 years in average). Thus, our famous faces might be closer in quality to personally known friends. However, the difference on rated emotionality for the two face types is significant if small. This finding shows that the hippocampus has a role in memory that is more general than only related to individual directly experienced events. In addition, retrieval of the types of stimuli proposed to be aided by the hippocampus is fast. We found reaction times of around 1250ms for famous faces and 1500ms for personally known faces on average, see Fig. 9.2. This argues against Conway et al.'s (1999) claim that whereas the hippocampus is involved in sensory-perceptual autobiographical memory, these have to be retrieved via more general autobiographical event knowledge, in a process that requires at least 5 seconds. The findings from this study show that, by contrast, autobiographical and indeed even public knowledge stimuli seem to automatically and strongly activate the hippocampus. It is possible that faces are particularly sensitive cues to facilitate the retrieval of vivid episodic memories,

or that hippocampal activation can reflect retrieval of less time-specific knowledge regarding familiar people.

A role for more emotional processing?

A further contributing factor to the better memory performance for personally known and famous faces might be that they are also more emotionally salient than unknown faces. We found significant activation in the amygdala, left orbitofrontal cortex, and bilateral insula as an effect of face type in Phase 2. The patterns of signal change in these areas are similar to those in the hippocampus, thus the signal is strongest for personally relevant faces and stronger for famous than for unknown faces. As discussed in the Introduction to Part II (Chapter 7), the amygdala plays a role in processing of emotional memories (Cahill & McGaugh, 1998; LeDoux, 2000) and has been shown to directly modulate hippocampal memory encoding (Hamann et al., 1999; Strange et al. 2004). The orbitofrontal cortex has been implicated in the retrieval of items from positive and negative emotional contexts (Maratos et al., 2001), and Piefke et al. (2003) suggested that this region may be preferentially engaged in the retrieval of autobiographical memories associated with positively valenced emotional context. Fink et al.'s PET experiment (1996) in which participants listened to sentences containing a familiar episode from their own or somebody else's autobiography, yielded right anterior insula activation in the comparison of personal versus impersonal autobiographical phrases. This was attributed to strong activation of the limbic system caused by the high emotional impact of the task.

The results from the post-scanning questionnaire are not entirely congruent with this role of emotional processing in memory retrieval for personally known and famous faces: Famous and personally known faces were rated rather neutrally on a behavioural level (1.67 and 2.35 on average for famous and personally known faces respectively, on a scale from -6 to +6). This might reflect that amygdala activation may not necessarily require strong emotions towards a stimulus per se but may also reflect more subtle links to emotion if related to personal experience. Further, note that we also found amygdala activation at *recognition* of famous and personally known stimuli in Phase 2. However,

percent signal change was higher for correctly rejected new versus remembered old items. This is in line with findings by Hamann et al. (1999), who reported enhanced amygdala activation at *encoding* for subsequently recognised pleasant, aversive or interesting as opposed to neutral pictures. The role of the amygdala in retrieval compared to encoding might be similar to that of the hippocampus, which is discussed below.

Hippocampal role in memory retrieval and (re-)encoding

The pattern of hippocampal activation during retrieval in the old-new recognition task shows that activation tends to be greater for (correctly rejected) new stimuli that are personally known than for (correctly recognised) old stimuli that are personally known, see Fig. 9.13b, p.136. Note that the fact that the hippocampus does not show an effect of interaction but only of face type means that the decrease from 'new' to 'old' is, strictly speaking, only a tendency, and not significant. Nonetheless, this tendency of repetition suppression has been reported elsewhere (Henson et al., 2003; Henson & Rugg, 2002), and could indicate involvement in recollection of old and possibly context-rich personal memories (as triggered by personally relevant faces) but not or much less in retrieval of a recently encoded stimulus presented on a neutral background, also indicated by the low amplitude of percent signal change for unknown faces hits (see also Fig. 9.13b). By contrast, structures that we find involved in the latter kind of retrieval are medial-dorsal thalamus, in accord with Aggleton & Brown's theory(1999), caudate, and right-sided prefrontal cortical structures.

Hippocampal activation on the other hand accompanied *successful (re-)encoding* for personally known and famous faces in Phase 1. In other words, the identification of personally known and famous faces in Phase 1 could be seen as reflecting retrieval as much as new encoding. Nonetheless, the success of this encoding is corroborated by the strong effect of superiority of recognition memory for personally known and famous faces. Further, we could hypothesise that hippocampal activation in Phase 2 could again signify re-encoding of the new personally known and famous pictures and *"re-re-encoding"* of the trace of the old pictures. Thereby the tendency of repetition

suppression could reflect a decreasing extent of new traces being formed when the event content has only changed slightly since the recent re-encoding. Strictly, we should corroborate this notion by looking for greater activation for subsequent hits than subsequent misses. However, in this experiment there were not many misses and this comparison could not be performed.

Memory age and the hippocampus

Pursuing further the exact role of the hippocampus in memory retrieval cued by different face types, this section discusses the finding that left hippocampal activation is modulated by the length of time a face was known for. A few recent studies have also reported that memory age modulates hippocampal activity (Addis et al. 2004; Maguire & Frith 2003; Piefke et al. 2003). It was generally found that more recent memories activate the hippocampus more strongly. However, Gilboa et al. (2004) argued that the crucial characteristic mediating the involvement of the hippocampus in remote autobiographical memory was *vividness.* Vividness often correlates negatively with memory age. E.g. Haist et al. (2001) using blocked fMRI, found remembering famous faces from the 1990's to lead to increased neural activity in the hippocampus bilaterally, whereas remembering famous faces from more remote decades didn't. On the other hand, it is very possible that "old" friends of our young participants might yield more vivid memories than recent acquaintances.

Our finding would further contradict an exclusive role of the anterior hippocampus in novelty detection (Strange et al., 1999) but be in line with a more widespread hippocampal representation for older friends through many incidents of "new memory re-encoding" in concordance with the multiple trace theory (Nadel & Moscovitch, 1997). Finally, the presence of strong hippocampal activation for retrieval of old memories and moreover a positive correlation with memory age (memory age was about 7 years for famous faces and 5 years for personally known faces in average) stands against the traditional idea of a time-limited hippocampal role in memory retrieval (Squire & Alvarez, 1995), at least within the time frames considered in this investigation.

Chapter 9

Conclusion

This study looked at the effect of personal relevance in stimulus material on brain activation during memory retrieval. Stimuli consisted either of faces that belonged to friends, famous people, or were unknown. Two retrieval settings were investigated: In Phase 1, subjects identified faces as friends or famous, in Phase 2 they recognised faces seen in Phase 1 from all three categories (personally known, famous or unknown). As a main result we found the hippocampus strongly activated in Phases 1 and 2 upon presentation of a familiar face (famous or personally known) as compared to an unknown face. Additionally, other areas were activated in this comparison that have been associated with contextual episodic memory retrieval (Burgess et al., 2001b; King et al., 2005; see Maguire, 2001a for an overview), namely dorsolateral prefrontal cortex, medial prefrontal cortex, anterior cingulate, temporoparietal junction and retrosplenium. In the hippocampus and in these areas, the predominant pattern of signal change was that the personally known faces produced the strongest activation, and famous faces stronger activation than unknown faces. This broadly parallels the amount of information (including facts and life-episodes) likely to be associated with each face. At the same time, the only region to yield a significant difference in the direct comparison between recognition of a personally known face and recognition of a famous face is the anterior prefrontal cortex (BA10). This is well in line with previous reports of its involvement in self-relevant processing (e.g. Cabeza et al. 2004; Craik et al., 1999; Levine et al., 1998; Maguire, 2001a; Maguire et al., 2001b; Wicker et al., 2003, see Introduction to Part II, Chapter 7, for a review). In addition, the activation in the left hippocampus correlates with the length of time a face is known for.

Chapter 10) An fMRI investigation of retrieval of spatial versus olfactory context in episodic memory

Introduction

We were curious to investigate the neural correlates of multimodal contextual memory with a specific focus on the role of the hippocampus. Some authors have suggested that the hippocampus provides a means of forming associations between information presented in different modalities or stored in different brain regions (e.g. Alvarez & Squire 1994; Damasio, 1989a; Marr, 1971; Mayes et al., 2001; Paller, 2002) and that this is required for episodic memory. To this end, we added olfactory context to a virtual reality paradigm used previously to assess context-dependent episodic memory (Chapter 8, see also King et al., in press). Olfactory perception and thus olfactory cue processing is different in important ways from processing of, for example, visual information. The behavioural characteristics of odour memory have already been discussed in the Introduction to Part II (Chapter 7). Here I briefly introduce the neural aspects of odour processing, before moving on to introducing the fMRI experiment presented in this chapter.

One distinctive aspect of odour processing is that limbic structures, which otherwise represent a late stage in sensory information processing, are involved in passive olfactory perception (Savic et al., 2000). The olfactory tract, besides projecting ipsilaterally to the piriform cortex (the caudolateral aspect of the orbitofrontal cortex at the frontotemporal junction, extending to the anterior dorsomedial aspect of the temporal lobe), reaches the anterior cortical nucleus of the amygdala and the periamygdaloid and entorhinal cortices directly. From the olfactory cortex and amygdala the third connection in the chain reaches targets in the rostral orbitofrontal cortex (BA 11), subiculum, thalamus, hypothalamus, brainstem and caudate nucleus (Powell et al., 1965, in Savic et al., 2000; and Carmichael et al., 1994, in Dade et al., 2002).

Further, both the piriform cortex and the amygdala also have direct connections with the anterior insular cortex (Mesulam & Mufshon, 1985; in Savic et al., 2000). In human

neuroimaging experiments orbitofrontal cortex, amygdala and insula have all been found to be activated by primary olfactory processing (Gottfried et al., 2002a,b; 2003; Royet et al., 2000; Sobel et al., 2000; Zald & Pardo, 1997; Zatorre et al., 1992). Perhaps in line with the direct limbic and orbitofrontal projections of olfactory processing regions, it has been found that the hedonic quality of smells is implicit in odour perception (Gottfried et al., 2002b; Schiffman, 1974). Also, the involvement of the limbic structures in even basic perceptual processing inspired an explanatory hypothesis for olfactory cues being particularly potent memory cues. There is some recent evidence in support of this 'Proust Phenomenon' (Chu & Downes, 2002; or Herz et al., 2004). However, it stands against a bulk of evidence against odours being particularly powerful reminders of the past (e.g. Bolger & Titchener, 1907; Davis, 1975; Herz, 1998; Rubin et al., 1984). As has been discussed in the Introduction to Part II (Chapter 7), odour identification and naming appears to be particularly inconsistent in humans (Cain & Potts, 1996; e.g. Engen & Ross, 1973). We found evidence for this in Chapter 8, ourselves. This might lead to the olfactory memory trace remaining more isolated in memory, thus more inaccessible but also more distinctive. In line with this, experimental evidence showed reduced retroactive interference in olfactory memory compared to other modalities (see Lawless & Engen, 1977; Rubin et al., 1984).

Note that the aim of this study was not to have olfactory and other memory cues compete. Rather, the focus of our interest was the neural network underlying successful memory retrieval across different modalities. Our particular interest was hippocampal involvement in memory retrieval of specific events via their association to an olfactory or spatial context. In order to counter the notorious volatility of semantic encoding in olfaction we tried to facilitate the encoding of olfactory context by choosing odours that were evaluated in pilot experiments to be familiar and easy to identify, as it has been shown that semantic integration of an odour enhances its success as a retrieval cue (Lawless & Engen, 1977; Lyman & McDaniel, 1990; Rabin & Cain, 1984).

The task used was congruent to the one in Chapter 8: Participants experienced a series of pseudo-realistic events simulated using a virtual reality paradigm (see King et al.,

2004). Subsequently, memories for various aspects of these events was probed using a context-dependent two-alternative forced choice paradigm: Pairs of objects were presented in a particular place, while at the same time an odour was delivered to subjects via plastic tubing. Two types of questions probed memories for the different elements of context; "Which object did you receive in this place?" and "Which object appeared with this smell?". Again, as in Chapter 8, an additional question-type probed familiarity for the object given. As we shall see, the task proved rather difficult for most subjects, many of whom did not perform significantly above chance. Only participants performing significantly above chance were however included in the fMRI analyses, and only correct trials were evaluated.

Materials and Methods

Participants:

24 right-handed healthy volunteers were scanned from whom 15 were selected (aged between 22 and 36 years, average = 26.1 years) on the basis of their performance in the contextual memory conditions (see *Procedure* below), requiring a score of ≥14 (of 24) items correct in both the odour *and* place conditions, for performance above chance. All subjects gave written consent according to the UCLH-ethics committee and were paid for participation.

Odour stimuli and odour delivery

The odour stimuli used are listed in Table 10.1. Extensive pilot experiments had shown that these odours were:

i) rated as familiar and can be described verbally (but note that odours are in general not easily labelled, see introduction, and our subjects did not generally come up with the veridical label),
ii) rated neutral in hedonic quality,
iii) matched in perceived medium intensity at the dilution ratios used,
iv) easily distinguished from each other.

Source	Common label for odour
Rose Maroc Essential Oil*, diluted 50% in Mineral Oil***	"Rose"
Spearmint Essential Oil**	"Spearmint"
Paraffin Oil (commercially available)	"Petrol", "Diesel", "White spirit"
Peanut Oil [from peanut jar (Sainsbury's)]	"Peanut butter"
Guaiacol***, diluted 2.5% in Mineral Oil***	"TCP", "Medicine"
Amyl Acetate***, diluted 1% in Mineral Oil***	"Pear drops", "Nail varnish remover"
Clove Essential Oil**	"Cloves"
Orange Essential Oil**, diluted 50% in Mineral Oil***	"Oranges"

Table 10.1 Odour stimuli used in experiment; source and common label.

* from Aqua Oleum (Stroud, UK); ** from Absolute Aromas (Planet Organic, Torrington Place, London); *** Sigma-Aldrich (Dorset, UK)

In the scanner, the odour stimuli were delivered by means of a ten-channel computer-controlled olfactometer that is suitable for the MRI environment and delivers odour pulses rapidly, without perceptible changes in tactile, auditory, or temperature features (Gottfried et al., 2002a). 8 channels were used to pass the air through chambers filled with odorous liquids. The two remaining channels contained solely air bubbled through distilled water. Airflow rates were set at 2.5 litres/min. At odour onset, a computer signal simultaneously closes a valve supplying normal room air (from a compressed air cylinder) and opens an odorised air valve. At odour offset the signal sequence is reversed, which reintroduces normal room air and provides rapid washout of residual odour in the tubing system.

Pre-scanning:

Familiarisation with odour stimuli, navigation procedure and places:

Participants were introduced to the odour stimuli from small brown bottles containing the odorous liquids, and attempted to name each odour. If they failed to find a name for a stimulus, the experimenter hinted towards the correct label so as to ensure all participants were familiar with the stimuli in the experiment and could confidently distinguish between them. They were thus introduced to the 8 odours used in the scanning experiment and additionally to 3 odours used in a practice trial.

Participants were then also shown the experimental virtual reality environment minus the stimulus containers. They were instructed to explore at random, but cued by the trainer to pass by all 8 locations featuring in the subsequent experiment.

Practise Trial:

Subjects were familiarised with the procedure of the study and test phase in a pre-scanning practise trial using the same virtual reality town but three different distinct locations, objects and odours within it.

Scanning experiment:

Study phase:

Subjects lay in the scanner with a respirometer attached to their chest and with a nasal canula nosepiece (diameter 3mm) with two endings directed into their nose, gently fixed next to their head. A stream of air from a compressed air bottle flowed trough the tube at all times. A virtual reality town (built on the commercially available computer game Deus Ex, the same town was also used in Chapter 8), was presented to the subjects via a mirror mounted on the head coil and a screen in the back of the scanner. Subjects navigated through the town using a button box following guiding icons through the town. These lead to a closed box (see Fig. 10.1), from which an object appeared when the subject approached within a radius of about 5 virtual meters. At the same time, the valve of the olfactometer was triggered as described above, and an odour stimulus was passed through the tubing system to the nose of the subject. 4s later the edges of the container turned red, which was the signal for the participant to walk towards the container to make the object disappear and turn off diffusion of the odour. The odour stream was switched back to neutral air after max. 5 s exposure time if the subject had not yet approached the container and object and thus triggered the odour (and object) to

Figure 10.1 Snapshot of the encoding phase. Following a trail the participant found a grey container. When the participant arrived close to it, an object appeared out of the container. At the same time an odour was diffused.

disappear. A new set of guiding icons then appeared, and the subject followed them to the next stimulus container. The study comprised 24 such events, each consisting of a randomly composed triad of 8 different locations, 8 different odours and 24 different objects, such that each object was used once and each place and odour three times. Each subject experienced unique combinations. The subjects were instructed to try and remember the odour and location of the appearance of each object and to breathe normally throughout the study phase.

Test phase:

Immediately after the study phase subjects were given a forced choice recognition memory test probing different aspects of memory, using the Cogent 2000 software suite (Wellcome Department of Imaging Neuroscience, London, UK), as implemented in MatLab 6.5 (The MathWorks Inc., Natick, MA). In each test trial subjects were shown an image of one of the box-locations from the study phase with two objects superimposed on the left and on the right of the screen, see Fig. 10.2. A question cue appearing on the top of the screen indicated what type of information was being probed. At the same time subjects were presented with an odour stimulus through the plastic tube. Subjects were instructed to sniff whenever a picture appeared and were given a green crosshair clue 900ms before upon which to prepare that sniff. The valve changing from odorised to normal air was triggered 450ms before the picture appeared. The subject responded as quickly and accurately as possible, using keys on the button box that was used for navigation during the study phase. The odorised air was changed to neutral air 2s after the picture appeared. The interstimulus interval was 10.08s.

In the odour condition, the question cue "went with smell" prompted subjects to indicate which object (left or right) occurred with the current odour stimulus, see Fig. 10.2a. In this case subjects ignored the presented container location, which would not be consistent with either object. The cue "went with place" prompted the subject to indicate whether the object on the left or right occurred at the shown location of the container, see Fig. 10.2b. Subjects ignored the simultaneously presented odour which would not be consistent with either object. Foil objects in these conditions as well as the perceptual

control condition (see below) were other objects from the study phase. In the object condition ("familiar object"), see Fig. 10.2c subjects indicated which of the two objects they had seen in the study phase. In this condition the foil objects were pictures of very similar objects taken from the same database (Hemera™ Photo Objects, Volume I). A perceptual control condition asked subjects which of the two objects was brighter ("brighter object"), see Fig. 10.2d. Finally, in a second control condition, "rest", they were shown no picture and given no odour stimulus and were simply prompted by the cross-hair to make a sniff. The sequence of question type was held constant, while object–foil pairings were randomised across subjects. The various conditions are summarised in Table 10.2. After the experiment subjects were asked about the strategies they used to memorise the places, odours and objects comprising each event.

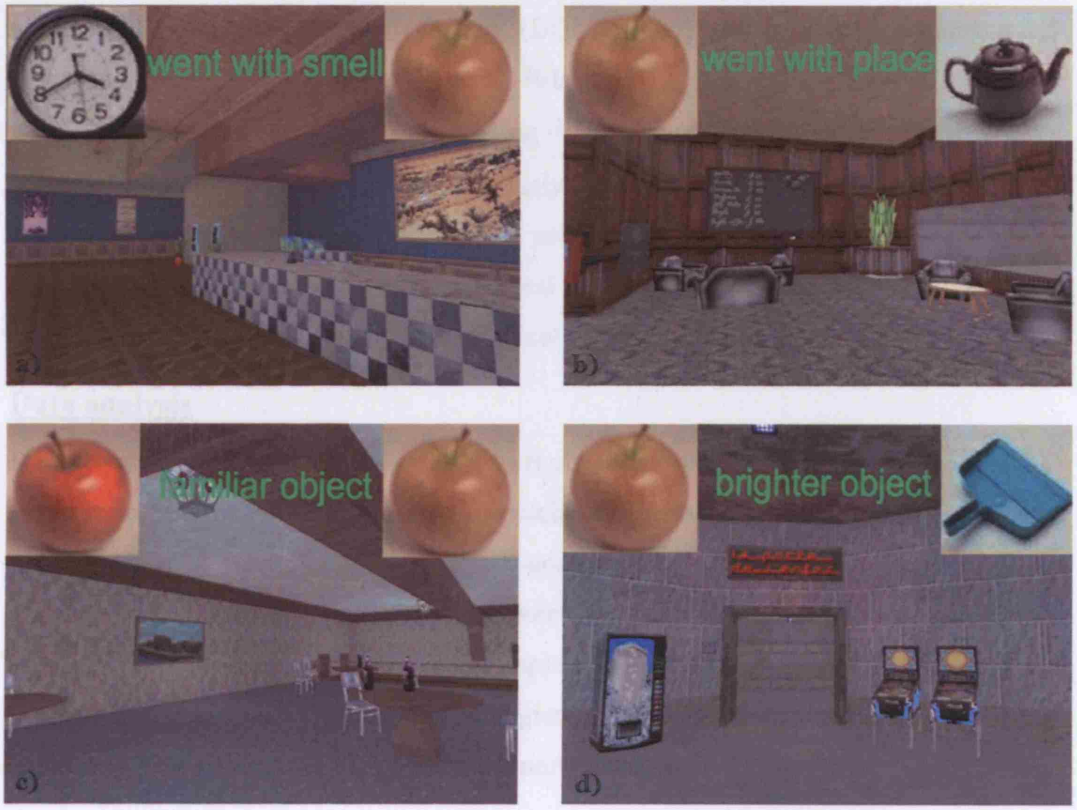


Figure 10.2 Visual stimuli for the three experimental conditions, a)-c), and control condition, d), in the recognition memory test (simultaneously with the visual stimulus an olfactory stimulus was also presented). **a)** Probing olfactory context "Which object went with this smell?" **b)** Probing spatial context: "Which object went with this place?" **c)** Probing familiarity-based object recognition: "Which of these objects is familiar?" **d)** Control question: "Which object is brighter?"

			Place-cue	Odour-cue	Objects
Experimental conditions	**context-dependent**	"Went with Smell"	✓ (irrelevant)	✓ (relevant)	both from study phase
		"Went with place"	✓ (relevant)	✓ (irrelevant)	both from study phase
	familiarity-based	"Familiar Object"	✓ (irrelevant)	✓ (irrelevant)	one from study phase, one new
Control conditions		"Brighter Object"	✓ (irrelevant)	✓ (irrelevant)	both from study phase
		"Null-Sniff"	×	×	none

Table 10.2 Summary of conditions of test phase.

fMRI scanning

40 T2*-weighted echoplanar images (EPI) per volume (3x3x3mm voxels; T_E = 90ms) with blood oxygenation level dependent (BOLD) contrast were acquired using a 1.5 Tesla Siemens VISION system (Siemens, Erlangen, Germany). EPIs consisted of 2mm thick slices oriented 30° from axial (spacing = 50 %), acquired in descending order. We collected a total of 345 volumes continuously with an effective repetition time (TR) of 3.6s with the first 5 volumes in each session being discarded to allow for T1 equilibration effects. T1-weighted structural images were additionally obtained after completion of the task (1.5x1.5x1.5 mm voxels, 3d acquisition).

Data analysis

Data from the recognition memory task (test phase only) were analysed using Statistical Parametric Mapping (SPM2 beta, with patches installed (30.1.03), for preprocessing, and SPM_devel, April 2004, Wellcome Department of Cognitive Neurology, UK, for the subsequent analysis). The T2-images were realigned, then spatially normalised to a standardised echo-planar image (EPI) template and smoothed (with a 8mm Gaussian kernel). The structural images were coregistered with the realigned mean functional image and then normalised using the same parameters.

For each subject, the fMRI time-series was high pass filtered (minimum cut-off period 128s), and modelled as the weighted sum of regressors corresponding to effects of interest. These included hits and misses for all memory conditions (2x3) plus the

"brighter object" condition, plus the "rest" condition which can be thought of as a null-event including sniffing. The regressors were defined as a series of stick-functions timed at 2s after the appearance of the test pictures on the screen. The timings were derived from logs produced by the Cogent presentation program. All regressors were convolved with the canonical haemodynamic response function. Further regressors based on estimates of head-movement, obtained from the realignment procedure, were included (to account for any second order effect of such movement remaining after realignment).

The parameters (i.e. the coefficients of the regressors) for the best fitting model were found, and subjected to a random effects analysis. The following contrasts were submitted to a t-test over all subjects: 'Bright>Null_sniff', 'Odour>Bright', 'Place> Bright', 'Object>Bright', 'Place>Odour', 'Odour>Place' in which only the regressors for the hits of the corresponding conditions were used. In an additional model, activation common to odour AND place-memory were evaluated by masking the t-image over all subjects of the 'Odour>Bright' contrast with a smoothed[1] (4mm) mask of the t-test over all subjects of the 'Place>Bright' contrast. The mask is 0 or 1 according to significance at FDR[2] 0.05, k_E=17. All results are reported at FDR=0.05, k_E =17, unless otherwise specified.

Results

Behavioural results:

There is a significant effect of condition (repeated measures ANOVA $F_{2,28}$=9.60, $p<0.001$) on memory performance, see Table 10.3. Paired t-tests reveal that odour memory performance is significantly worse than both place memory ($p<0.001$) and object memory ($p<0.005$) but that there is no difference between the object and place conditions ($p=0.20$).

[1] The mask was smoothed to reduce the risk of spurious activation occurring at the edge of the mask that is actually localised outside the region.
[2] False Discovery Rate, see Genovese et al. 2002

	Memory Condition		
	'Odour'	'Place'	'Object'
Average number correct (of 24)	17.4 (2.5)	20.6 (3.0)	20 (3.3)

Table 10.3 Average performance per memory condition ('Odour', 'Place' and 'Object'), standard deviation in brackets, n=15.

Reaction times also differ between the different memory conditions, (repeated measures ANOVA $F_{2,28}$=20.24, p<0.001), see Table 10.4. Paired t-tests indicate highest reaction times for odour memory ($p_{'Odour'>'Place'}$< 0.001, $p_{'Odour'>'Object'}$ <0.001). The difference in reaction times between the 'Place' and 'Object' condition is also significant ($p_{'Place'>'Object'}$ =0.017).

	Memory Condition			Control Condition
	'Odour'	'Place'	'Object'	'Bright'
Average reaction time	3698 ms (940 ms)	3027 ms (700 ms)	2748 ms (549 ms)	2315 ms (398 ms)

Table 10.4 Average reaction times for correct answers in different memory conditions ('Odour', 'Place' and 'Object') and control condition 'Bright', standard deviation in brackets, n=15.

Imaging results:

a. Control Condition 'Bright>Null_Sniff', see Table 10.5

The contrast of the control condition 'Bright' with the control condition 'Null_Sniff' captures primary odour perception and sniffing (i), in line with previous neuroimaging studies on olfactory perception (Gottfried et al., 2002a; Gottfried & Dolan, 2003; Royet et al., 2000; Sobel et al., 2000; Zald & Pardo, 1997), and other

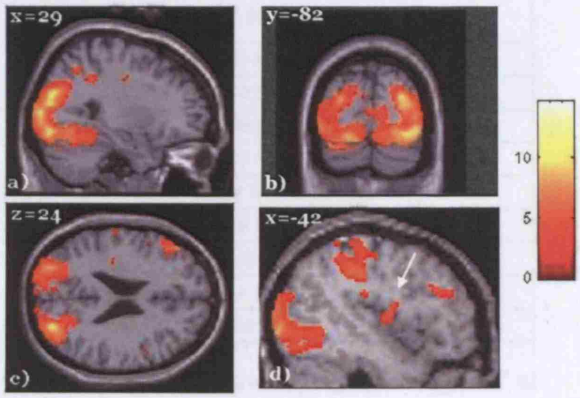


Figure 10.3 Various activation peaks showing in the control condition contrast '**Bright> Null_Sniff**' (rendered on one subject's normalised structural scan). **a) - c)**: Vast cuneus, lingual gyrus (extending to fusiform on the right) and cerebellar activation. **d)** Activation in the left insula.

cognitive processing unrelated to explicit contextual memory retrieval, e.g. involved in attention, object processing, deciding between two visual stimuli and responding, etc. (ii). It reveals

i) cerebellum (but see discussion), and insula (see Fig.10.3d)

ii) cuneus/ lingual gyrus (see Fig. 10.3a-c), fusiform (object recognition) area, various regions in prefrontal and cingulate cortex, and intraparietal sulcus (BA40/7).

Area			x,y,z (mm) of cluster-peak:	T-value	Voxel count k_E
bilat.	Lateral Middle Occipital Gyrus, extending to Inferior Occipital Gyrus, Intraparietal Sulcus, Cerebellum, Lingual Gyrus, on the right also extending to Fusiform Gyrus., **see Fig. 10.3a)-c)**	BA 19	-28 -92 14	14.71	15219
			34 -94 0	11.12	subpeak
L	Cerebellum	posterior medial-inferior	-12 -72 -44	3.58	22
bilat.	Intraparietal Sulcus	BA 40/ 7	-44 -32 36	6.73	1213
			28 -42 40	5.01	83
			34 -56 50	4.58	64
			52 -22 32	3.65	25
Posterior Cingulate		BA 23	-2 -14 30	5.57	96
			12 -34 30	4.51	24
R	Medial Superior Frontal Gyrus, extending contralat.	BA 6/ 8	6 2 58	6.79	725
L	Middle Frontal Gyrus /Superior Frontal Sulcus		-22 0 42	4.29	20
			-28 -2 54	3.66	17
bilat.	Dorsolateral Prefrontal Cortex	BA 46/ 9	-48 38 24	8.72	713
			50 20 30	4.35	93
			46 4 34	4.11	35
			46 38 20	3.7	26
bilat.	Insula, **see Fig. 10.3d)**	BA 13	-42 -6 0	4.06	91
			40 2 -2	3.51	26
			-36 -22 22	3.52	37

Table 10.5 Significant activation peaks in the control condition contrast **'Bright>Null_sniff'** at FDR = 0.05, k_E=17.

b. Activation of 'Odour' AND 'Place' (see Table 10.6 and Fig.s 10.4 and 10.5)

Activation areas common to both contextual memory retrieval conditions 'Odour' AND 'Place' are listed in Table 10.6 (the separate tables for 'Odour>Bright' and 'Place>Bright' follow in Tables 10.7 and 10.8 for the sake of completeness). They comprise retrosplenium/ posterior cingulate, precuneus, inferior parietal cortex (BA 39/19), fusiform gyrus, bilateral hippocampus and parahippocampal gyrus (see Fig.10.4), anterior cingulate, thalamus (see Fig. 10.5a, b, & d), bilateral dorsolateral prefrontal cortex (BA6 and BA9/46), right ventrolateral prefrontal cortex (BA 47),

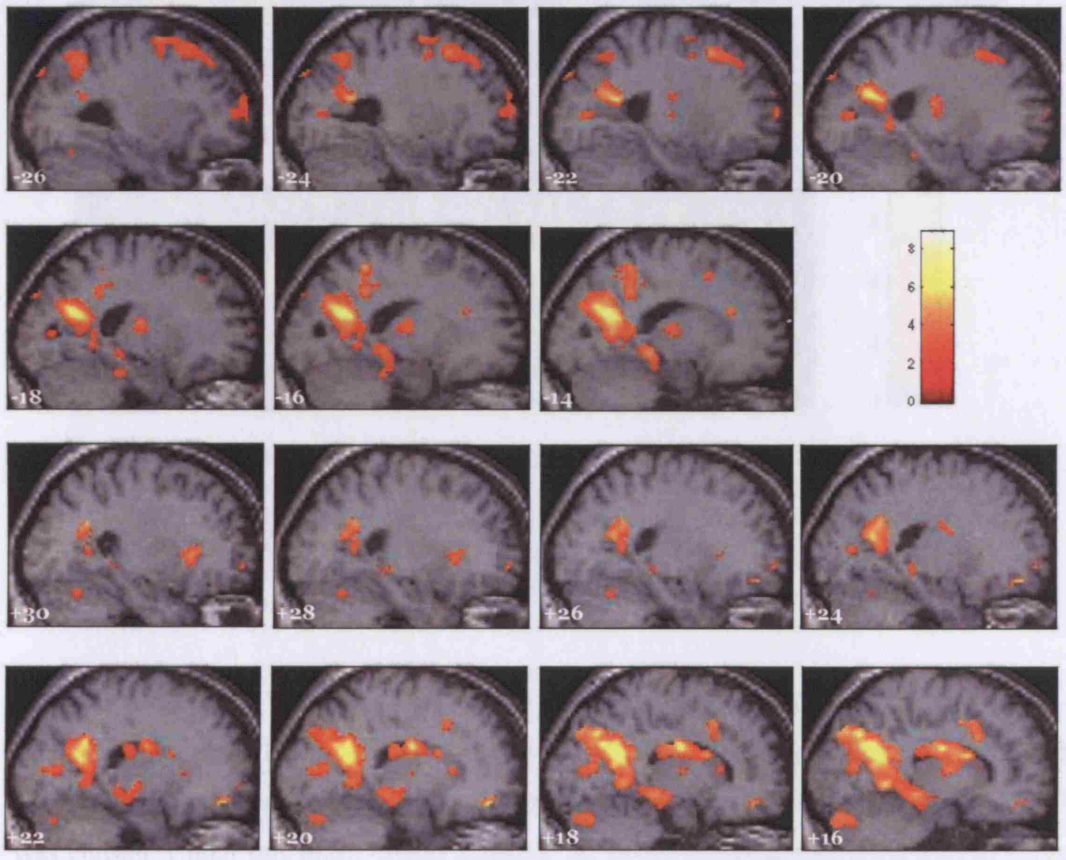


Figure 10.4 'Odour>Bright' AND 'Space>Bright' (contrast 'Odour>Bright', masked by 'Place>Bright'(smoothed (4mm) and thresholded at FDR 0.05, k_E=17), at FDR 0.05, k_E=17, rendered on one subject's normalised structural scan. Sagittal slices illustrating activation of interest in the medial temporal lobe.

anterior prefrontal cortex (BA10, see Fig. 10.5c), substantia nigra (see Fig. 10.5e) and cerebellum. This activation network can be interpreted as an "episodic memory retrieval network beyond modality". In line with this, many activation peaks directly overlap with areas reported by Burgess et al. (2001b) and King et al. (in press) in context-dependent episodic memory retrieval using a similar paradigm, see Table 10.6, last column.

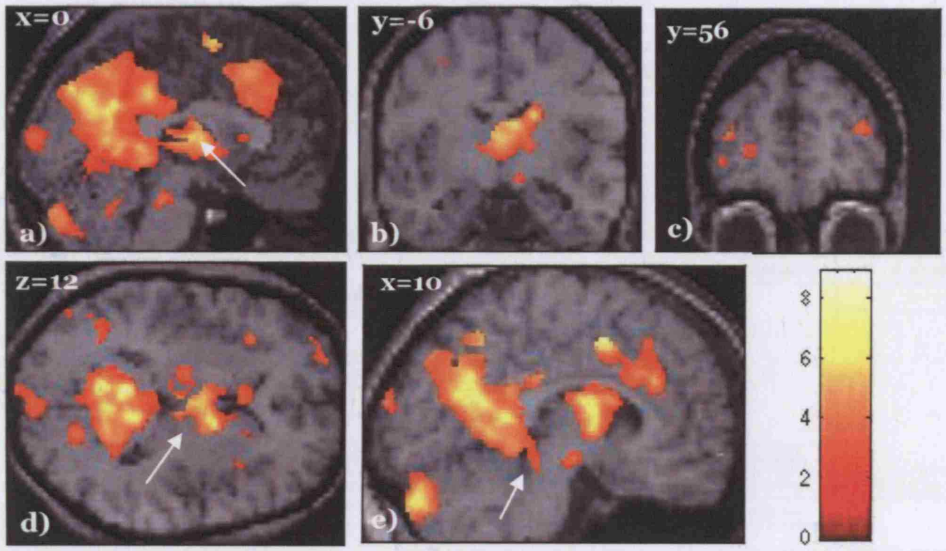


Figure 10.5 'Odour' > 'Bright' AND 'Space'>'Bright' (contrast 'Odour>Bright', masked by 'Place>Bright'(smoothed (4mm) and thresholded at FDR 0.05, k=17), at FDR 0.05, k_E=17, rendered on one subject's normalised structural scan. **a), b) & d)**: Bilateral thalamus. **c)** Lateral tip of prefrontal cortex (BA 10), bilaterally. **d)** Substantia nigra.

c. 'Odour>Place', 'Place>Odour' (see Tables 10.9 and 10.10)

Tables 10.9 and 10.10 report activation in the contrasts 'Odour>Place' and 'Place>Odour' respectively. For both contrasts, the lower threshold of $p<0.001$, k_E=9 was chosen. Under this more liberal marginal value we limit our interpretations to areas for which prior hypotheses exist, with a primary focus on the medial temporal lobe. We find hippocampal activation in both contrasts. The contrast 'Odour>Place' yields right posterior hippocampal activation, whereas the reverse contrast, 'Place>Odour' yields bilateral hippocampal activation more anteriorly. This is further illustrated in Fig. 10.6,

Area			x,y,z (mm) of cluster-peak:	T-value	Voxel count k_E	Corresp. peaks in Burgess et al. (2001) place>percept	Corresp. peaks in King et al. (in press) place>percept and person>percept
bilat.	Retrosplenium/ Posterior Cingulate	BA 29/ 30/ 23	-6 -48 8	8.89	14416*	-6 -30 30 (within)	-9 -78 36 (within)
			6 -56 18	7.92	subpeak	3 -69 30 (within)	9 -48 42 (within)
bilat.	Precuneus	BA 31/ 18	-12 -64 20	8.56	subpeak	-15 -60 18 (within)	
			-42 -72 38	7.05	subpeak		-33 -84 27 (adjacent)
			16 -70 36	6.38	subpeak		
bilat.	Cuneus	BA 18/ 17	6 -100 18	5.03	254		
			-20 -76 4	3.39	44		
			20 -80 6	3.35	subpeak of above		
bilat.	Inferior Parietal Lobule	BA 39/ 19	-40 -62 38	7.8	subpeak of above	-27 -72 39 (within)	-33 -54 39 (within)
			46 -70 38	3.73	159	42 -75 39 (adjacent)	
bilat.	Fusiform Gyrus		-48 -42 0	3.5	subpeak of above	-24 -69 -9 (within)	
			36 -50 2	3.02	subpeak of above		
bilat.	Parahippocampal Gyrus, **see Fig. 10.4**		-28 -44 -14	9.27	subpeak of above	-2 -42 -15 (within)	
			26 -40 -14	5.87	subpeak of above	24 -33 -18 (within)	
R	Parahippocampal Gyrus extending to Hippocampus, **see Fig. 10.4**		22 -14 -4	3.08	subpeak of above		18 -30 -9 (within)
L	Posterior Hippocampus, **see Fig. 10.4**		-18 -24 -8	4.19	subpeak of above	-21 -27 -6 (adjacent)	-21 -27 -6 (adjacent)
bilat	Thalamus, including Ventrolateral Nucleus, **see Fig. 10.5a),b) & d)**		0 -6 12	5.65	subpeak of above		-15 -12 6 (within)
bilat.	Caudate		14 10 18	6.37	subpeak of above		
			-8 20 10	3.22	41		
L	Posterior Middle Temporal Gyrus	BA 22	-64 -38 2	3.81	156		
bilat.	Cingulate Gyrus, extending to Dorsomedial Prefrontal Cortex	BA 32/ 24/ 8	8 6 46	7.78	1591		
			6 30 48	5.8	subpeak		
L	Anterior Cingulate	BA 24	-12 30 24	4.29	29	-6 21 39 (adjacent)	
bilat	Dorsolat. Prefrontal Cortex, leaking into Anterior Insula on the left	BA 9/ 46/ 45 & BA 13	-54 22 28	7.04	969	-48 27 21(within)	-48 24 21 (within)
			48 26 28	5.26	237	52 30 30 (within)	
R	Insula, posterior tip	BA 13 and BA 47	36 -26 24	5.82	108		
	Insula, leaking into Putamen medially and extending to Ventrolateral Prefrontal Cortex anteriolaterally		38 26 2	5.16	277	30 24 -6 (within)	30 24 -15 (near)
			20 22 6	3.19	subpeak		
R	Dorsomedial Prefrontal Cortex, ext. contralaterally	BA 6	2 4 66	6.77	126		
L	Middle Frontal Gyrus/ Dorsolateral Prefrontal Cortex		-30 2 60	6.08	554	-36 15 57 (adjacent)	-24 21 42 (adjacent)
R	Orbitofrontal Cortex	BA 11	22 48 -16	5.79	59		
bilat	Lateral tip of Prefrontal Cortex, **see Fig. 10.5c)**	BA 10	36 54 20	4.2	122		
			-36 58 14	4.18	197	-27 51 -3 (adjacent)	-39 57 0 (within)
R	Ventral Superior Frontal Gyrus		30 62 -8	3.51	28	30 57 3 (near)	30 60 -6 (within)
R	Substantia Nigra, **see Fig.10.5e)**		10 -10 -10	3.89	subpeak		15 -15 -12 (within)
bilat.	Cerebellum	posterior medial, ext. contralat.	-6 -86 -40	7.24	885		-9 -81 -33 (adjacent)
			8 -84 -30	6.75	subpeak		12 -75 -27 (adjacent)
		post. lateral	44 -76 -32	6.01	347		
		posterior	-28 -68 -24	3.63	20		
		anterior medial	0 -54 -28	3.31	37		

Table 10.6 Significant activation common to both **'Odour>Bright' AND 'Space>Bright'** (contrast 'Odour>Bright', masked by 'Place>Bright'(smoothed (4mm) and thresholded at FDR 0.05, k_E=17), at FDR 0.05, k_E=17. The last two columns show corresponding activation peaks found in Burgess et al. (2001) and King et al. (in press).

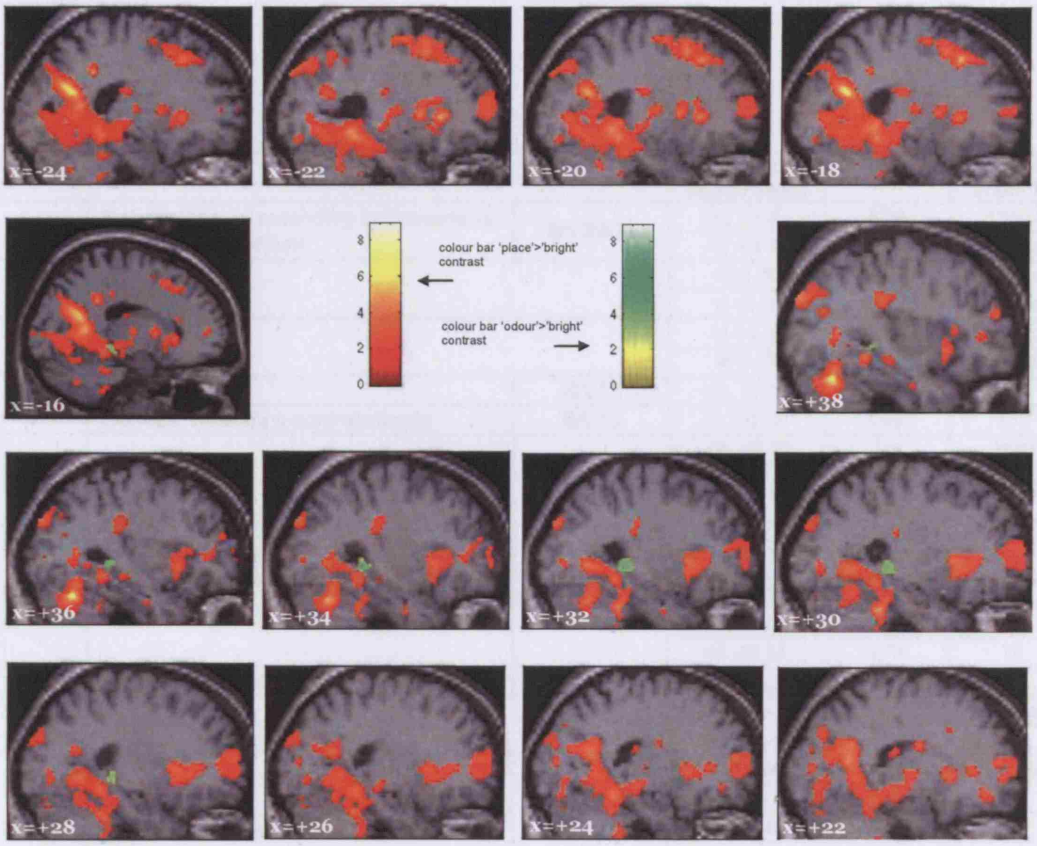


Figure 10.6 Hippocampal activation cluster of 'Odour>Bright' contrast (in green) on 'Place>Bright' contrast (both FDR 0.05, k_E=17), rendered on one subject's normalised structural scan. Illustrative overlay of hippocampal activation for selected sagittal slices. It shows that hippocampal activation is disparate in the two modally different contextual memory conditions, and stronger for odour on the right and place on the left.

in which the hippocampal activation from the 'Odour>Bright' contrast is superimposed on the 'Place>Bright' contrast. The pronounced hippocampal activation in both contextual memory conditions shown complements the more moderate hippocampal activation in the conjunction, see **b.** above. Thus, we find that the overlap of hippocampal activation in the two conditions is rather small compared to the broad but disparate activation peaks in both contextual memory conditions. In addition, the 'Odour>Place' contrast shows activation in the left insula, known to mediate olfactory processing, whereas the 'Place>Odour' contrast reveals areas along the ventral stream of visual processing, including fusiform and parahippocampal cortices, and lateral temporal regions.

Area			x,y,z (mm) of cluster-peak:	T-value	Voxel count k_E
bilat.	Retrosplenium, extending to Precuneus, Cuneus, Cerebellum	BA 29/31	-6 -46 8	8.89	13523
			-12 -64 20	8.56	subpeak
bilat.	Thalamus		8 -2 18	6.71	subpeak
			-8 -2 12	5.17	subpeak
bilat.	Caudate		14 10 18	6.37	subpeak
			-6 6 22	5.03	subpeak
R	Precuneus	BA 23	16 -72 10	4.06	55
R	Cuneus, extending contralaterally	BA 18	6 -100 18	5.03	187
bilat.	Angular Gyrus, extending to Superior Temporal Gyrus, Postcentral Gyrus (Temporoparietal Junction)	BA 39/40/22	-40 -62 38	7.8	2050
			-62 -50 18	5.84	subpeak
			-54 -28 22	3.83	21
			62 -58 22	4.52	54
			64 -16 2	4.19	13
			58 -52 38	4.04	23
			68 -24 22	3.76	58
			46 -70 38	3.73	75
R	Precentral Gyrus	BA 4	34 -30 60	5.04	51
bilat.	Tail of Hippocampus		-16 -30 -8	3.98	subpeak
			32 -34 -4	4.01	90
bilat.	Dorsolateral Prefrontal Cortex	BA 6/8	8 -18 54	8.44	subpeak
			44 -6 42	5.56	50
			46 24 46	3.87	53
			54 2 46	3.67	56
			-30 2 60	6.08	408
bilat.	Lateral Prefrontal Cortex	BA 9/44 and BA 46	-54 22 28	7.04	785
			-56 4 14	4.45	27
			48 28 28	5.28	221
			34 16 22	3.62	32
bilat.	Anterior Lateral Prefrontal Cortex	BA 9/10	36 54 20	4.2	36
bilat.	Anterior Orbital Gyrus	BA 11	22 48 -16	5.79	62
			-22 30 -18	4.22	19
R	Insula, posterior tip	BA 13	36 -26 24	5.82	64
	Anterior Insula		38 26 2	5.16	157
bilat.	Posterior Cerebellum	medial, extending contralat.	-8 -86 -40	7.94	749
			8 -84 -30	6.75	subpeak
R		superior lateral	44 -76 -32	6.01	98
		inferior lateral ext. towards medial	38 -74 -50	4.9	108
			34 -60 -26	3.71	68
L	Pons		-4 -26 -24	4.85	121
R	Substantia Nigra		10 -10 -10	3.69	17

Table 10.7 Significant activation peaks in the contrast **'Odour>Bright'**, FDR=0.05, k_E=17.

Area			x,y,z (mm) of cluster-peak:	T-value	Voxel count k_E
bilat.	Cerebellum	posterior lobe	38 -62 -28	12.92	27439
			26 -42 -30	6.2	subpeak
		anterior lateral	-26 -54 -28	3.92	subpeak
		anterior medial	2 -54 -26	8.69	subpeak
		lateral anterior inferior	-16 -38 -46	4.16	42
bilat.	Parahippocampal Gyrus, extending to Fusiform & Lingual Gyrus		26 -40 -14	5.87	subpeak of above
			-28 -44 -14	9.27	subpeak of above
bilat.	Hippocampus		-18 -24 -14	3.84	subpeak of above
			38 -22 -14	3.61	37
	Cuneus, extending contralaterally	BA 18	8 -98 8	6.43	subpeak of above
R	Middle Occipital Gyrus	BA 19/37	52 -76 12	3.81	32
	Precuneus	BA 23/31	0 -64 28	4.82	subpeak of above
L	Posterior Cingulate, ext. contralaterally	BA 31	-12 -40 52	4.39	subpeak of above
bilat.	Precuneus/ Angular Gyrus	BA 19/39	-38 -80 38	10.75	subpeak of above
			48 -70 30	6.84	789
bilat.	Retrosplenium	BA 18	-6 -48 4	8.04	subpeak of above
			8 -58 8	8.9	subpeak of above
bilat.	Basal Ganglia	BA 25	0 8 0	10.1	subpeak of above
bilat.	Thalamus		4 -2 4	6.03	subpeak of above
			-14 -14	5.62	subpeak of above
bilat.	Caudate		12 6 14	4.9	subpeak of above
			-12 6 4	5.49	subpeak of above
			-14 30 18	4.44	31
		posterior tip	-20 -18 20	4.03	52
bilat.	Dorsolateral Prefrontal Cortex	BA 8/ BA 6	-20 24 44	7.72	788
		BA 9	50 30 36	4.72	76
		BA 6/4	2 4 66	3.76	24
R	Anterior Lateral Prefrontal Cortex	BA 10	14 66 2	5.36	655
R	Intraparietal Sulcus	BA 40/7	40 -28 30	5.3	141
bilat.	Superior and Middle Temporal Gyrus	BA 22/21	-48 -24 -10	5.17	127
			-52 2 -26	3.88	29
			58 -38 -12	4.83	61
R	Cingulate Gyrus	BA 32	18 18 34	4.36	74

Table 10.8 Significant activation peaks in the contrast **'Place>Bright'**, FDR=0.05, k_E=17.

Area			x,y,z (mm) of cluster-peak:	T-value	Voxel count k_E
bilat.	Precuneus	BA 7/31	10 -68 32	7.77	74
			12 -60 30	4.52	subpeak
			-10 -64 40	6.12	20
L	Angular Gyrus	BA 39	-42 -60 36	4.31	10
L	Splenium	BA 23	-10 -36 20	6.18	30
bilat.	Supramarginal Gyrus/ Temporoparietal Junction	BA 40	-48 -54 22	6.51	51
			-60 -44 32	4.96	48
			64 -24 22	5.57	67
			62 -42 26	4.4	13
R	Postcentral Gyrus	BA 3	22 -42 58	4.97	14
			20 -32 52	4.01	23
L	Medial Dorsal Superior Frontal Gyrus, extending contralaterally	BA 6/8	-2 12 64*	8.55	807
			0 20 48*	7.13	subpeak
			0 6 58*	6.82	subpeak
bilat.	Dorsolateral Prefrontal Cortex	BA 6/46/9	-56 2 18	5.42	85
			-50 32 24	5.23	85
			-54 24 30	5.08	subpeak
			-42 30 38	5.09	23
			60 2 36	5.32	22
R	Striatum Pericalcarine		30 -48 16	5.33	20
L	Thalamus	Pulvinar	-18 -22 8	4.78	9
R	Tail of Hippocampus		30 -28 -2	4.66	21
L	Insula	BA 13	-36 6 18	4.39	10

Table 10.9 Significant activation peaks in the contrast **'Odour>Place'** at lowered threshold of p< 0.001, uncorr., k_E=9. (*: survive threshold FDR 0.05, k_E=17)

Area			x,y,z (mm) of cluster-peak:	T-value	Voxel count k_E
bilat.	Occipital Lobe	BA 19, extending to BA 39	40 -84 24	6.83	131
			26 -88 24	4.23	subpeak
			-38 -78 20	4.64	70
			-38 -84 30	4.42	subpeak
bilat.	Fusiform Gyrus/ Parahippocampal Gyrus	BA 35/36/37	-28 -42 -18	6.48	301
			-18 -38 -14	5.38	subpeak
			24 -38 -20	5.82	202
			-42 -34 -16	4.64	9
			26 -52 -8	4.27	subpeak
bilat.	Hippocampus		26 -20 -24	5.99	31
			-30 -22 -20	4.72	18
bilat.	Posterior Cingulate, extending to Lingual Gyrus	BA 30/ BA 17/ BA 18	16 -58 14	6.23	50
			22 -88 -4	4.74	10
			-12 -72 0	5.86	184
			-14 -58 10	5.74	subpeak
R	Superior Temporal Gyrus / Temporal Pole	BA 38	38 16 -38	5.85	48

Table 10.10 Contrast **'Place>Odour'** at lowered threshold of p< 0.001, uncorr., k_E=9
(continued next page)

R	Posterior Inferior Temporal Gyrus	BA 37	64 -56 -10	4.57	13
bilat.	Lentiform Nucleus	Putamen	-18 12 -6	5.85	65
			22 14 2	5.58	57
			20 10 -10	4.22	13
R	Pons		10 -32 -36	5.79	301
R	Midbrain	Red Nucleus	6 -20 -2	4.94	27
R	Cerebellum	Culmen, Anterior Lobe	44 -46 -28	5.69	60
		Cerebellar Tonsil, Posterior Lobe	26 -30 -42	4.19	12
L	Anterior Cingulate extending to Medial Frontal Gyrus	BA 32/ BA10	0 42 -6	4.38	81
			-8 34 -4	4.03	subpeak
			-10 48 0	4.24	30
			-6 56 -2	4.06	subpeak

Table 10.10 continued

d. 'Odour>Object' and 'Place>Object' (see Table 10.11)

Both, the 'Place>Object' and the 'Odour>Object' contrasts compare a condition that necessarily involves contextual recollection with a condition that could be solved solely on the basis of familiarity-based recognition. Accordingly, we might expect to find activation in support of the distinction between recollection and familiarity-based recognition (Aggleton & Brown, 1999), that is, anterior thalamus and hippocampus. In support of this, we find right hippocampus (see Fig. 10.7a, b, & d) and anterior thalamus (see Fig. 10.7e), however only when using a more liberal threshold of k_E=9 (at FDR = 0.05). The strong parahippocampal and fusiform activation in the

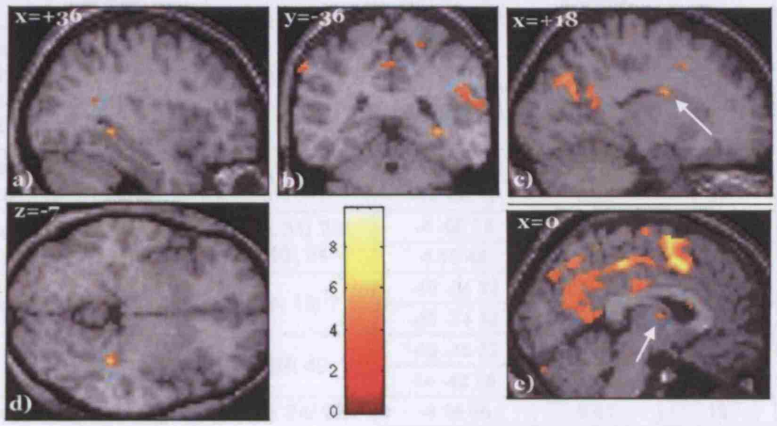


Figure 10.7 Various activation peaks in the contrast **'Odour>Object'**, FDR=0.05, k_E=17 (exc. thalamus **(e)**, k_E=9), rendered on one subject's normalised structural scan. **a),b) & d)** Right hippocampus. **c)** Caudate nucleus. **e)** Anterior thalamus.

'Place>Object' condition (see Fig. 10.8a, b, & d) we interpret as neural basis of place-processing (the ventral stream).

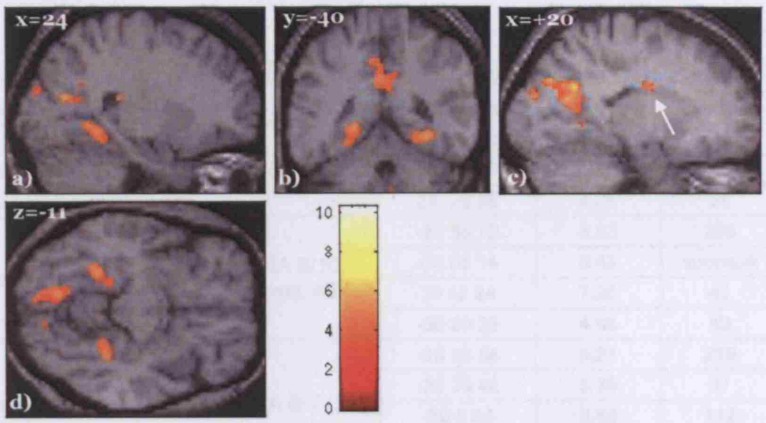


Figure 10.8 Contrast **'Place>Object'**, FDR=0.05, k_E=17, rendered on one subject's normalised structural scan. **a),b)** & **d)** Parahippocampal gyrus, extending to fusiform gyrus. **c)** Caudate nucleus.

There are further significantly activated areas in the 'Place>'Object contrast, most probably corresponding to visual processing (BA31/30/18/17/19/7). In both the 'Odour>Object' and the 'Place>Object' contrast there are additional more extended retrosplenial and surrounding posterior regions as well as prefrontal regions, in line with the greater difficulty and reliance on recollection of the 'Odour'- and 'Place'-cued memory tasks as compared to the 'Object' memory task. In addition, and intriguingly congruent in both contrasts, the right caudate is also active (see Fig.s 10.7c and 10.8c).

Contrast	Area			x,y,z (mm) of cluster-peak:	T-value	Voxel count k_E
space>object	L	Precuneus, ext. contralat.; Cingulate Gyrus; Retrosplenium, ext. Cuneus	BA 31/ 30/ 18	-12 -68 22	10.33	5374
				-10 -28 44	9.56	subpeak
				-10 -52 12	8.79	subpeak
				-12 -94 9	7.18	subpeak
odour>object	bilat.	Cuneus/ Middle Occipital Gyrus	BA 18/ 17	10 -96 6	4.34	51
				-12 -92 -2	5.25	37
odour>object	L, ext. bilat.	Posterior. Cingulate ext. to Anterior Cingulate	BA 31/ 23/ 30/ 24	-4 -60 28	9.85	3598
				4 12 48	9.21	subpeak
space>object	L	Superior Occipital Gyrus	BA 19/ 7	-40 -84 32	7.22	740
odour>object				-40 -74 42	7.67	810
space>object	L	Angular Gyrus	BA 40	-46 -48 32	4.21	41
odour>object	R	Supramarginal Gyrus		64 -42 26	4.45	47
space>object	bilat.	Anterior Cingulate Gyrus	BA 24/ 32	-4 14 46	5.41	19

Table 10.11 Combined table of significant activation peaks in **'Place>Object' and 'Odour>Object'** contrasts. Both at FDR=0.05, k_E=17 (exc. thalamus: k_E=9). – continued next page

odour>object				4 -10 34	6.54	242
odour>object	R	Postcentral Gyrus, ext. to Subcentral Gyrus	BA 1/ 2, ext. BA 40	66 -16 30	6.97	426
				48 -32 24	5.91	subpeak
odour>object	R	Precentral Gyrus	BA 6/ 4	20 -22 68	5.54	26
				46 -10 40	5.49	117
				24 -28 56	4.25	35
space>object	bilat.	Lateral Prefrontal Cortex	BA 9/10, ext. 46	-20 56 12	8.55	269
				-36 56 14	6.88	subpeak
				30 42 24	7.26	42
				-50 20 26	4.98	43
space>object	L	Dorsolateral Prefrontal Cortex	BA 6/ 8/ 9/ 44	-18 16 54	8.21	219
				-26 36 42	5.39	37
odour>object				-30 6 60	6.68	112
				-50 24 36	6.35	217
				-58 4 14	5.21	22
odour>object	R	Medial Superior Frontal Gyrus, ext. contralat.	BA 6	6 -10 68	5.22	78
space>object	L	Posterior Middle Temporal Gyrus	BA 21/37	-60 -46 -4	4.83	24
space>object	bilat.	Parahippocampal Gyrus, extending to Fusiform Gyrus on the right		-20 -38 -4	6.38	291
				-26 -46 -10	5.45	subpeak
				-22 -34 -16	4.63	subpeak
				34 -38 -8	6.21	250
				26 -46 -6	5.48	subpeak
				26 -54 -2	5.39	subpeak
odour>object	R	Tail of Hippocampus, see Fig. 10.7a),b) & d)		36 -36 -6	6.43	26
space>object	R	Caudate, see Fig. 10.7c), 10.8c)		20 -4 26	4.30	17
odour>object				18 0 24	5.82	21
odour>object	L	Anterior Thalamus, see Fig. 10.7e)		0 -2 8	4.34	9
space>object	L	Insula	BA 13	-28 20 -4	4.18	24
space>object	R	Cerebellum	anterior lateral	44 -44 -40	4.14	22
odour>object			posterior medial	4 -84 -30	4.63	74
			Inf. post. lat.	26 -82 -50	4.4	9

Table 10.11 continued

e. 'Object>Odour' and 'Object>Place' (see Table 10.12)

The areas activated in the 'Object>Odour' and 'Object>'Place contrast are perhaps not so much correlates of familiarity-based recognition as of new encoding taking place. Note that these are the only contrasts involving new visual stimuli (the novel foil objects). The contrasts reveal a predominantly right-sided network of occipital (see Fig. 10.9a & b) with limbic (amygdala, see Fig. 10.9d) and orbitofrontal activation (see Fig.10.9d & e). This is interpreted as reflecting the neural basis of new encoding of objects with an olfactory and visuospatial context.

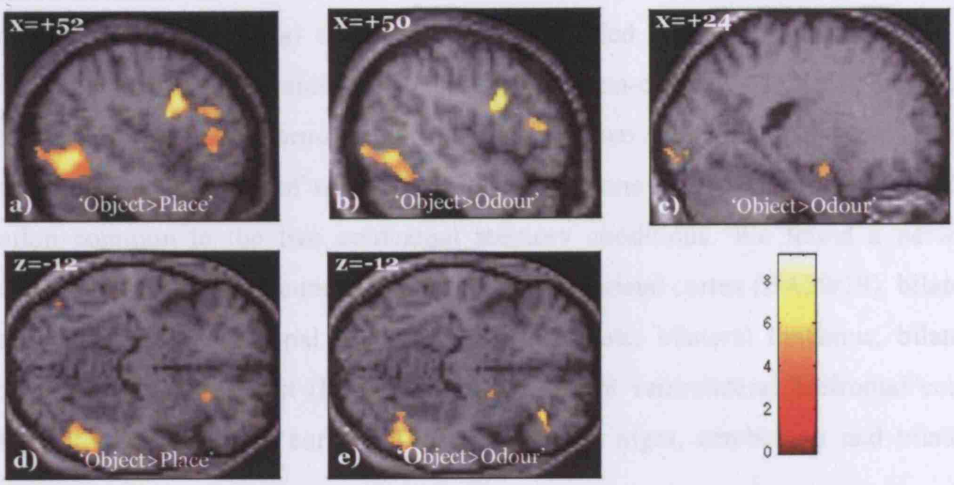


Figure 10.9 Various activation peaks in **'Object>Place'** and **'Object>Odour'** contrasts, FDR=0.05, k_E=17, rendered on one subject's normalised structural scan. **a) & b)** Extensive right occipito-temporal as well as lateral inferior frontal activation. **c)** Right amygdala. **d) & e)** Right orbitofrontal activation.

Contrast	Area			x,y,z (mm) of cluster-peak:	T-value	Voxel count k_E
object > odour	R	Dorsolateral Prefrontal Cortex	BA 9	52 10 26	9.17	226
object>place	R	Inferior Lateral Prefrontal Cortex, see Fig. 10.9a) & b)	BA 44/ 46/ 45	50 12 24	9.88	309
				54 28 20	7.18	86
object > odour				50 34 4	5.62	70
				50 34 10	5.74	46
object>place	bilat.	Orbitofrontal Cortex, see Fig. 10.9d) & e)	BA 11/47	22 26 -14	5.63	35
object > odour				36 36 -12	6.38	45
object>place	bilat.	Posterior Lateral Temporal Lobe	BA 37/ 19	58 -50 -10	6.34	subpeak of 52,-58,-10
				-42 -74 -2	5.43	63
object>place	R	Middle Occipital Gyrus towards Posterior Middle Temporal Lobe, see Fig. 10.9a) & d)	BA 19/ 37	52 -58 -10	9.46	689
				44 -82 -4	6.75	subpeak
object > odour	R	Occipital Lobe, see Fig. 10.9b) & e)	BA 19/ 18	50 -60 -12	7.18	479
				36 -84 -8	7.04	52
object > odour	R	Amygdala, see Fig. 10.9c)		22 -2 -16	5.04	45
object > odour	bilat.	Putamen		20 2 -8	4.75	subpeak of 22,-2,-16

Table 10.12 Combined table of significant activation peaks in **'Object>Place'** and **'Object>Odour'** contrasts. Both at FDR=0.05, k_E=17.

Summary of Results

Behaviourally, the contextual condition 'Odour' yielded lower performance than the other contextual memory condition 'Place' and the non-contextual object recognition condition ('Object'). Performance in the latter two conditions did not differ significantly. On the level of neural activity, on the one hand we were interested in activation common to the two contextual memory conditions. We found a network including retrosplenium, precuneus, bilateral inferior parietal cortex (BA39/19), bilateral fusiform and parahippocampal gyrus, anterior cingulate, bilateral thalamus, bilateral dorsolateral prefrontal cortex (BA6 and BA9/46), right ventrolateral prefrontal cortex (BA47), anterior prefrontal cortex (BA10), substantia nigra, cerebellum and bilateral hippocampus.

On the other hand, we were interested in activation specific to the context-modality, with a focus on the hippocampus and found that the direct comparison 'Odour>Place' yielded right posterior hippocampal activation, whereas 'Place>Odour' yielded bilateral more anterior hippocampal activation. This picture was completed by more modality-specific activation, in the left insula for the 'Odour>Place' condition, and bilateral activation along the ventral stream of visual processing, including fusiform, parahippocampal cortices, and lateral temporal regions, in the 'Place>Odour' contrast. Thus, there is *overlapping* activation in the hippocampus for the two contextual memory conditions, but there are also disparate activation loci, showing in the direct comparison between the two conditions.

Furthermore, contrasting the two contextual memory conditions with the familiarity-based object recognition condition, we find hippocampal and anterior thalamic activation, consistent with the hypothesis of Aggleton & Brown (1999).

On the other hand, we contrasted the object recognition condition with the two contextual conditions. The 'Object' condition is the only condition including new visual stimuli (the foil objects). We predominantly found activation supporting processing of

new material, i.e. right-lateralised occipital, amygdala, and orbitofrontal activation, but not the hippocampus.

Finally, we found significant cerebellar activation in the 'Bright>Null_sniff' contrast as well as in the conjunction of 'Odour>Bright' AND 'Place>Bright', in the 'Place>Object' and in the 'Odour>Object' contrast.

Discussion

This study investigated the neural basis of multimodal context-dependent memory using a virtual reality environment for the creation and test of spatial contexts, and an olfactometer that delivered additional olfactory context. We were particularly interested in the networks common to memory cued by spatial context and memory cued by olfactory context, and also looked at modality-specific activation, with a focus on the hippocampus. In addition, context-dependent memory retrieval was contrasted with familiarity-based object recognition. These results are discussed with regard to previous findings below.

Episodic memory retrieval network beyond context-modality

Significantly active areas common to olfactory AND spatial context-dependent memory included retrosplenium/ posterior cingulate, precuneus, inferior parietal cortex (BA39/19), bilateral fusiform gyrus, hippocampus and parahippocampal gyrus, anterior cingulate, bilateral dorsolateral prefrontal cortex (BA6 and BA9/46), right ventrolateral prefrontal cortex (BA47), anterior ventral prefrontal cortex (BA10) and cerebellum. This network is largely congruent with the "episodic memory network" as previously found by Burgess et al. (2001b), King et al. (in press) and others (see Maguire, 2001a for a review). Moreover, interestingly, these areas are mostly congruent with regions that were previously found specifically in spatial context-dependent memory. On the basis of these new findings they can now be interpreted as an episodic memory network exceeding the visuo-spatial modality.

With regard to the hippocampus, we found that the conjunction of olfactory AND spatial context-dependent memory yielded more left posterior activation compared to Burgess et al. (2001b) and King et al. (in press). Further, this experiment and King et al.'s (in press) study found more extensive right hippocampal activation than did Burgess et al. (2001b) This could have to do with the more recent studies involving more distinct contexts for each episode compared to Burgess et al.'s (2001b) experiment. In terms of lateralisation we definitely find significant *bilateral* hippocampal activation for context-dependent episodic memory, not only for the spatial context but also for the conjunction of odour-cued AND place-cued memory retrieval. This contradicts the notion of an exclusive role of the right hippocampus in spatial and left hippocampus in episodic memory. This lateralisation issue is further discussed in the Discussion of Part II (Chapter 11).

Further evidence for non-spatial right-lateralised hippocampal activation comes from the results of modality-specific memory retrieval:

Modality-specific memory retrieval

The direct comparison 'Odour>Place' yielded right posterior hippocampal activation. On the other hand, the comparison 'Place>Odour' revealed activation bilaterally, more anteriorly compared to the 'Odour>Place'-peak. These disparate activation peaks depending on modality complement the above finding of a common hippocampal activation peak *independent* of context-modality. The modality-specific comparisons further revealed left insula specific to the odour context, consistent with previously reported involvement of this region in odour naming (Qureshy et al., 2000) and other odour processing (Gottfried et al., 2002a; Gottfried & Dolan, 2003; Royet et al., 2000; Sobel et al., 2000; Zald & Pardo, 1997), and activation along the ventral visual stream including the parahippocampus specific to the spatial context, further in line with reports of its role in spatial processing, especially landmark recognition (Aguirre et al., 1998; Aguirre & D'Esposito, 1999; Bohbot et al., 1998; Epstein & Kanwisher, 1998; Habib & Sirigu, 1987; Johnsrude et al., 1999; Maguire et al., 1996b; Maguire et al., 1998b) as discussed in the Introduction to Part I (Chapter 2).

Recollection versus familiarity-based recognition

In accord with the proposed distinction between neural bases for recollection and familiarity (Aggleton & Brown, 1999), we would expect to find activation in the anterior thalamus and hippocampus in the conditions that rely on recollection and cannot be solved on the basis of pure stimulus familiarity, i.e. 'Odour' and 'Place', as compared to 'Object'. On the other hand, the reverse contrasts ('Object>Odour' and 'Object>Place') might reveal parahippocampal and dorsolateral thalamus activation, supporting familiarity-based recognition (Aggleton & Brown, 1999). However, the possibility remains that the object task could be solved using recollection and thus the effect might be diminished. Our data supports the first notion: The 'Odour>Object' contrast yielded activation in the anterior thalamus and right hippocampus. By contrast, the areas activated in the contrasts, 'Object>Odour' and 'Object>Place', do not reveal neural correlates of familiarity-based recognition; A predominantly right-sided network of occipital with limbic and orbitofrontal activation is hypothesised to mediate new encoding of objects within olfactory and visuospatial contexts. This interpretation is suggested by the fact that the object condition is the only one to involve new stimuli.

Cerebellar activation ("beyond sniffing")

Although the cerebellum is not the main focus of interest in this investigation, the very prominent cerebellar activation found in various contrasts (involving the conjunction 'Odour>Bright' AND 'Place>Bright', 'Bright>Null_Sniff', 'Place>Object' and 'Odour>Object') deserves a brief discussion. Given that all conditions involve olfactory processing, this cerebellar activation might be attributable to sniffing: Sobel et al. (1998) demonstrated that cerebellar (motor) activity is different depending on whether there is an odorant, even if sniffing occurs in all conditions. Moreover, they found significant activation in the lateral middle to posterior cerebellum during the "no sniff" phase of the sniffing task, which may be related to an inhibitory process of suppressing olfactory input (Laing, 1983). This part of the cerebellum is thus expected to modulate the amount of odour intake, maintaining the inverse proportionality between sniff volume and odour concentration.

Interestingly, sniffing activity cannot account for all cerebellar activation found in our study: Even if the strong activation in the 'Object>Bright' contrast (compared to the 'Odour> 'Bright' -contrast, see Fig. 10.10d versus 10.10b) might reflect a very similar inhibitory mechanism as found by Sobel et al. (1998), the strong activation seen particularly in the 'Place>Bright' (see Fig. 10.10c), and in the conjunction of 'Place>Bright' AND 'Odour>Bright', is more likely to be of the kind reported by Andreasen et al. (1999) when subjects retrieved a past episode, or by Fink et al. (1996) when hearing sentences describing a familiar episode from one's past. In support of this hypothesis, all activation peaks reported by Andreasen et al. (1999) lie within or adjacent to the activation we report, see Table 10.14. Importantly,

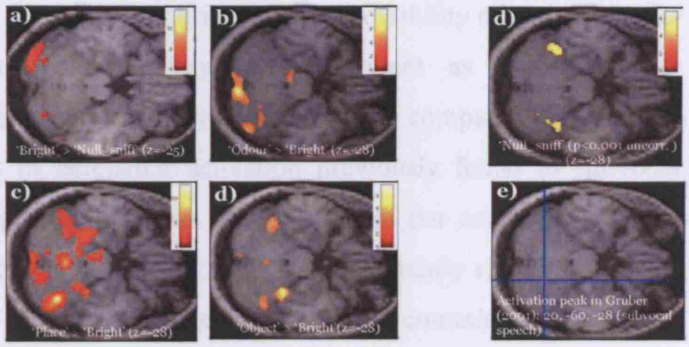


Figure 10.10 Cerebellar activation in different conditions. Contrasts are thresholded at FDR 0.05, (exc. d, 'Null_sniff'; p< 0.001 uncorr. – note that this effect of interest only represents residual variance not captured by any other contrasts. Rendered on one subject's normalised structural scan.

Location within Cerebellum	x,y,z (mm) of cluster-peak:	Voxel count k_E	Corresp. activ. peak in Andreasen et al. (1999)
Posterior Medial Cerebellum, extending contralaterally	-6 -86 -40	885	19,-75,-23 (adjacent)
	8 -84 -30	subpeak	
Right Lateral Posterior Cerebellum	44 -76 -32	347	34,-55,-32 (within)
			40, -60, -4 (near)
Left Posterior Lobe	-28 -66 -24	20	
Anterior Medial Cerebellum	0 -54 -28	37	42,-66,-23 (adjacent)
Left Lateral Cerebellum	-36, -46, -30	31	-46,-58,-30 (near)

Table 10.13 Comparison of **cerebellar activation** peaks in conjunction contrast 'Odour>Bright' AND 'Place>Bright' (see Table 10.6 for details) with peaks reported by Andreasen et al. (1999) in the episodic memory condition.

Andreasen et al. (1999) in their study had controlled for the possibility of activation due to subvocal speech, showing minimal laryngeal movement as recorded with electroglottalography in the episodic memory retrieval task compared to a silent counting task. Also, the locus of cerebellar activation previously found in subvocal speech (Gruber, 2001), see Fig. 10.10e, is not congruent with our activation pattern. Andreasen et al. (1999) and Fink et al. (1996) argue that the mainly right hemisphere cerebellar activation is part of an interactive network with the contralateral prefrontal cortex engaged in coordinating the conscious retrieval of memory.

Conclusion

This study involved a virtual reality design for the presentation and test of context-rich events and simultaneous odour-delivery enabling the study of multi-modal context-dependent memories. For context-dependent memory independent of context-modality, we found significant activation in bilateral hippocampus and adjacent parahippocampal gyri together with a wider network of episodic memory retrieval as previously established (Burgess et al. 2001b; King et al., in press; see Maguire, 2001a for an overview). Complementing the finding of overlapping hippocampal activation independent of context modality, we found the hippocampi further significantly activated in disparate areas for contextual memory retrieval specific to 'Odour' and 'Place' respectively, in the right posterior hippocampus in the 'Odour>Place' comparison, and bilaterally more anteriorly for the 'Place>Odour' comparison. Compared to a non-contextual object recognition condition, both context-dependent conditions 'Odour' and 'Place' yielded further hippocampal and additional anterior thalamic activation in support of a neural dissociation between context-dependent recollection versus familiarity-based recognition memory (Aggleton & Brown, 1999).

Chapter 11) Discussion Part II

For half a century the medial temporal lobes and the hippocampus in particular have been implicated in the acquisition of new memories (Scoville and Milner, 1957). 30 years ago this position was refined to suggest that, more specifically, the hippocampus is essential for the kind of memory that is remembered including a rich contextual specification (Kinsbourne & Wood, 1975), 'episodic memory' (Tulving (1972, 1983), in contrast to memory for facts (semantic memory). Today, the various contemporary theories on memory systems, as reviewed in the General Introduction (Chapter 1), agree that "whatever else it may do, the human hippocampus supports this episodic type of memory" (Burgess et al., 2002, p. 632). Recently, evidence was provided that the acquisition of semantic memory might be possible without intact hippocampal functioning (Vargha-Khadem et al. 1997). However, the interplay between episodic and semantic memory is still not entirely clear. Furthermore, although demonstrations exist showing contextual episodic memory retrieval to be hippocampal-dependent while familiarity-based recognition may not be (King et al. 2004, but see also Squire & Zola 1998), as hypothesised by the dual process theory (Aggleton & Brown 1999), it remains to define how the different aspects of context are bound together in episodic memory, and whether they are stored and retrieved independently or holistically.

Early functional neuroimaging evidence for hippocampal involvement in episodic memory retrieval remained puzzlingly absent or at least unreliable (e.g. Shallice et al., 1994; Tulving et al., 1994b). One factor that might play a role in this could be a lack of truly multimodal contextual memories in laboratory experiments as compared to real life. Also, the hippocampus might be specifically involved in personally relevant episodic memory – a hypothesis supported by the fact that neuroimaging studies on autobiographical memory invariably yield hippocampal activity (Addis et al., 2004; Cabeza et al. 2004; Maguire & Mummery 1999; Maguire et al. 2000; Gilboa et al. 2004; Piefke et al., 2003; Ryan et al. 2001)? A third line of argument is that the hippocampus has an important role at encoding as much as at retrieval and thus, in a contrast between old and new items in a recognition paradigm, there will be no differential activation in

the hippocampus, engaged in encoding the new stimuli (Fletcher et al. 1997). In the following I aim to provide evidence in support of some of the above hypotheses on the basis of the findings gathered in the experiments of Part II of this thesis.

Further evidence for selective hippocampal involvement in context-dependent memory as compared to familiarity-based recognition

The results from both Chapter 9 and 10 further corroborate the notion that the hippocampus is involved in context-rich memory retrieval and not familiarity-based recognition (see also King et al. 2004): In Chapter 9 we even found a decrease of signal change between a correctly rejected new stimulus and a recognised old stimulus (for famous and personally known faces), and no hippocampal involvement in the recognition of unknown faces. By contrast, we found evidence for increased activation in the medial dorsal thalamus for unknown recognised faces, as part of the familiarity-based recognition axis according to Aggleton & Brown (1999). Chapter 10 yielded selective involvement of the hippocampus in context-dependent memory retrieval (the 'Odour' condition) compared to a memory condition that could be solved on the basis of familiarity (the 'Object' condition), mirroring findings by Burgess et al. (2001b) and King et al. (in press) regarding the spatial context condition and repeated in this study.

How are the different aspects of an event bound together in episodic memory?

In Chapter 8 we established that the various aspects of an event's context act as independent retrieval cues. Thus it seems as if the different elements of an event were encoded and retrieved independently. Whereas one could argue that this was dependent on a setting where a series of similarly composed virtual reality events are encoded and subsequently probed via different cues, evidence for the validity of this finding beyond the virtual reality setting comes from a longitudinal study of real-life memories (Wagenaar 1986). Further, in Chapter 10 we found that different contextual aspects of such virtually created events yielded hippocampal activation in different subregions; the olfactory cue in contrast to the spatial cue led to more posterior and more right-sided activation. In addition, in Experiment II of Chapter 8 and the experiment of Chapter 10 we saw a significant difference in the effectiveness of different contextual cues.

Especially the odour cue lagged behind the others in retrieval success. Taken at face value, retrieval cue inequalities contradict one idea of the Cognitive Map theory (O'Keefe & Nadel 1978). There it was hypothesised that elements of episodic memory, thought to be organised in a map-like memory system, would be retrievable symmetrically by each other. By contrast, and this has been hypothesised earlier already (Morton et al., 1985; Morton & Bekerian, 1986), some cues are clearly preferred over others. In our study, Chapter 8, this was the 'person' cue over the 'place' or 'odour' cue. Further, retrieval symmetry seems related to the strength of a formed association (see also Wichawut & Martin, 1971), and one important factor mediating association strength appears to be the semantic embedding of the contextual aspect. As has been shown in Chapter 8, retrieval success of an individual olfactory cue was correlated with the "nameability" of the odour. This leads us to the question of the interplay between semantics and episodic memory.

Semantic embedding of episodic memory – supported by the hippocampus?

Aside from the correlation between verbal encoding of an odour (interpreted as an indication of its semantic anchoring) and its retrieval success as an episodic memory cue, we also found anecdotal evidence from post-experimental reports for participants using semantic relationships to encode together the different aspects of a virtual reality event in the experiment of Chapter 8. Note that this contrasts with the lack of evidence for verbal encoding in a previous study (Burgess et al. 2001b). It may be amplified by the additional demands of the odour cue in the study presented here. The results in Chapter 9 also relate to the effect of semantic embedding of the contents of episodic memory. We found that subjects showed a performance advantage for recognising faces from a study list, when the faces were familiar (personally known or famous), thus embedded in personal or more public semantic memory. This effect is well established in cognitive psychology. What is remarkable is that the hippocampus shows differential activation for the retrieval of known faces compared to unknown faces in an old/new recognition situation, even if the faces are not from an autobiographical stock (famous faces). Thus, on the one hand abstracted semantic information is thought to be represented outside of the hippocampus (Graham & Hodges, 1997; Hodges &

McCarthy, 1995; Tulving 1983; Tulving & Markowitsch 1998; Vargha-Khadem et al. 1997), namely in the anterior and lateral temporal lobes, which yielded strong bilateral activation for familiar (personally known and famous) compared to unknown faces in the fMRI study of Chapter 9. On the other hand, they nonetheless support retrieval success in an old/new recognition test, which is correlated with stronger hippocampal activation. This finding resembles the recently reported evidence for a recognition performance advantage for famous faces rated high in personal significance in semantic dementia patients (Westmacott et al. 2004). They both support the notion of a strong episodic-semantic interconnection in healthy memory function. Overall, we suggest that, although episodic memory and facts can be retrieved independently, retrieval from episodic memory is usually supported by the semantic associations of the contents of each event, and this relies on an interplay between hippocampus and lateral temporal lobe.

The potential of famous faces to trigger hippocampal-dependent memory retrieval leads us to the discussion of the results of Part II with regard to the role of personal relevance in episodic memory:

Vividness rather than personal relevance drives hippocampal activation in memory

On the one hand, the direct comparison between memory retrieval by personally known versus famous faces (Chapter 9) revealed activation not in the hippocampus, but in the anterior medial prefrontal cortex (BA10). On the other hand, we found strong hippocampal activation in the retrieval of episodic memory consisting of elements of a virtual reality setting (Chapter 10). We would hypothesise that the virtual reality episodes experienced by the participants were not of great personal *relevance*, despite the fact that the experiencing was active and personal, possibly slightly more than for example the study of a list of words. In concordance with Gilboa et al. (2004), who found that retrieval of detailed vivid autobiographical experiences as opposed to personal semantic information was found to be a crucial feature determining the involvement of the hippocampus (and not memory age), we would argue that the essential feature that correlates with a memory being both truly episodic and at the same

time strongly hippocampal-dependent is *vividness.* This is in line with our finding of stronger (left) hippocampal activation for personally known faces that were known for longer. The notion of vividness is further more adequate as a defining characteristic of the multi-modal event-memories retrieved in Chapter 10 under prominent affordance of hippocampal activation.

A last point of discussion constitutes the hippocampal involvement in encoding the new:

Is there ever retrieval or is it always re-encoding?

Fletcher's (1997) argument that hippocampal activation in fMRI experiments would cancel in the contrast between recognised old stimuli and new encoded novel stimuli has been corroborated in a study by Strange et al. (1999), reporting significant hippocampal activation for stimulus novelty. There is an interesting finding from the study reported in Chapter 9 relating to this phenomenon. Whereas familiar (personally known and famous) faces triggered hippocampal activation in the old/new recognition experiment both for remembered old and correctly rejected new stimuli, the activation decreased slightly for old compared to new. The finding of repetition suppression has been reported elsewhere (Henson et al., 2003; Henson & Rugg, 2002). Note that it implies a faintly different interpretation of hippocampal function compared to "novelty detection", namely it supposes that a rich (vivid) network of memory units, activated by a cue, is extended by a further aspect from the current event. The non-finding of hippocampal activation in the contrast between a condition involving new stimuli ('Object') and a context-dependent memory condition in Chapter 10, further supports the interpretation that the role of the hippocampus is not novelty detection per se but the integration of the new elements into the memory network. The lack of hippocampal activation in the abovementioned contrast is complemented by a strong hippocampal signal in the inverse contrast of a context-dependent memory condition with the 'Object' condition. Although this finding is consistent with a hippocampal role in context-dependent memory rather than familiarity-based recognition, it is also possible that this activation reflects the re-binding of the contextual elements including the new situation. In this sense, it would also be consistent with the multiple trace theory (Nadel & Moscovitch 1987).

Chapter 11

Conclusion

In summary, the experiments of Part II confirmed the hippocampal involvement in cross-modal, vivid, contextual-rich episodic memory (as compared to familiarity-based recognition), but underlined the dense collaboration of the hippocampus with lateral temporal lobe structures (the semantic memory network) to provide superior memory retrieval for semantically well-embedded memory items. They further showed that personal relevance of memories is not necessarily mediated by the hippocampus but rather by the anterior medial prefrontal cortex. Finally they suggest that the role of the hippocampus is neither exclusively the retrieval of the old nor the encoding of the new, but may also reflect the binding of the new contextual elements with the content of episodic memories, and integration into the existing information network stored in the brain. The access of the network elements appears however influenced by the differential strength of connection between them, such that mutual retrieval success is asymmetrical.

Chapter 12) General Discussion

The final chapter of this thesis addresses what our explorations into spatial (Part I) and episodic (Part II) memory have taught us about the function of the hippocampus, and how their findings can be brought together. - Do the results from our topographical memory paradigm (Chapters 3 to 5) add anything to the interpretation of the results from the episodic memory investigations in Chapters 8 to 10? In what way if any, do the insights from the analysis of binding structures in episodic memory (Chapter 8) inform our understanding of topographical memory? Do the fMRI findings from Chapters 9 and 10 have implications for the contemporary theories of memory systems as discussed in Chapter 1? What do they add to the question of lateralisation of hippocampal function? What ideas for future experiments result from combinations of the research approaches followed in Part I and Part II respectively?

We started off from the viewpoint of the Cognitive Map theory (O'Keefe & Nadel 1978), hypothesising a human hippocampal function in allocentric spatial memory, which might be selectively supported by the right hemisphere. We further supposed a role of the left hippocampus in episodic memory (Burgess et al. 2002). This kind of memory we contrasted with familiarity-based recognition on the one hand, which in turn we hypothesised to be supported by parahippocampal structures adjacent to but separate from the hippocampus (Aggleton & Brown 1999), and from semantic memory, the neural basis of which we would assign to the anterior and lateral temporal lobes (e.g. Graham et al. 2003; Hodges & McCarthy, 1995). In the following I discuss whether we found further evidence for the lateralisation hypothesis, and try to bring together the findings on the 'spatial' and 'episodic' aspects of hippocampal memory function and explore how they could inform each other.

The riddle of lateralised human hippocampal function

The only finding from Part I relating to the question of lateralisation of human hippocampal function is the dissociation of topographical disorientation, which we showed to correspond to an allocentric spatial representation deficit, and intact verbal

recall in an elderly patient, C.F., with probable early Alzheimer's disease (Chapter 4). This dissociation is however more reminiscent of O'Keefe & Nadel's (1978) original proposal of a lateralisation along a verbal-spatial than a spatial-episodic axis as hypothesised by Burgess et al. (2002). Further, structural data did not show any visible changes in either temporal lobe to the current date.

From Part II we have functional neuroimaging data on a possible lateralisation of hippocampal function in *episodic* memory. What is the evidence? - Chapter 9 revealed bilateral hippocampal involvement in the retrieval of autobiographical memory as cued by personally known faces. Note that whereas other autobiographical memory studies reported prevailingly left-lateralised activation, (see Maguire 2001a for a review), as Graham et al. (2003) argued, the neuropsychological literature supports the finding that right-sided or bilateral temporal lesions significantly impair autobiographical memory retrieval. Further, Graham et al. (2003) proposed that retrieval of an autobiographical memory may initially recruit *left* temporal structures (during the hypothesised processing of the meaning of the cue word and retrieval of life time period, around initial 1-12s of the retrieval process) and later be more dependent on the *right* temporal lobe (hypothesised to be involved in the production of recollective experience of a specific episode, from 15-30s of the retrieval process). However, an alternative interpretation for our finding of left *and* right hippocampal activation in autobiographical memory retrieved by personally known faces would be that the left hippocampus covers the retrieval of episodic information, whereas the right side would be activated more specifically in response to the face stimulus. Other studies have found the right hippocampus involved in the recognition of familiar faces (Leveroni et al. 2000), and Simons et al. (2001, experiment 1) also reported a significant correlation between atrophy in the right hippocampus but not left and impairment on the recognition memory test for faces (Warrington, 1984). Episodic memory retrieval cued by faces might thus be an interesting exception to the rule of left-lateralised episodic memory function in the human hippocampus.

In Chapter 10 we investigated retrieval of episodic (context-dependent) memory without using faces. We again found evidence in favour of a right-hippocampal participation in non-spatial episodic memory: bilateral hippocampal activation in context-dependent memory, in the overlap of both modalities 'Place' and 'Odour'; bilateral hippocampal activation in the direct contrast 'Place>Odour' with a dispersion along the rostro-caudal axis; and right hippocampal activation in the reverse comparison of 'Odour>Place'. Note that these data are in line with findings of a previous version of our virtual reality paradigm, involving a person cue instead of an odour cue: King et al. (in press) found right hippocampal activation in the spatial context-dependent memory condition compared to a control condition. Although one could hypothesise that, as with faces, the spatial cue might itself be right lateralised, this is not consistent with Burgess et al.'s (2001b) findings of left hippocampal activation in the place-cued memory condition.

Given the apparent additional involvement of the right hippocampus in episodic memory, is there also evidence for a left-hippocampal involvement in spatial memory? In fact, evidence from neuroimaging on spatial memory tasks is also not unequivocally in favour of an exclusively right-hemispherical involvement of the hippocampus in spatial navigation: Ghaem et al. (1997) found bilateral hippocampal activation in mentalised navigation compared to rest, and left hippocampal activation in the contrast between mentalised navigation and landmark imagery. Hartley et al. (2003) found right hippocampal activation to correlate with navigation success within subjects, but bilateral (left-biased) hippocampal activation to correlate with navigation success across subjects. Maguire et al. (1998a) found right hippocampal activation to correlate with wayfinding accuracy, but the contrast between successful and unsuccessful navigation also yielded left hippocampal activation.

On the basis of these findings I would like to make the following hypothesis, under the reservation that fMRI results might not be entirely suitable to answer the lateralisation question due to the possibility of leaking of activation to the other hemisphere through strong interhemispheric connections, and that these findings need to be complemented by neuropsychological studies which might inform us about which structures are not

merely involved but necessary for spatial or episodic memory function respectively. Similar to the proposed lateralisation of face perception by Simons et al. (2003), I would propose a role for the right hippocampus in perceptual and conceptual features of spatial and episodic memory and a role for the left hippocampus in narrative aspects, see Fig. 12.1. This would be broadly consistent with the verbal/ visuo-spatial distinction derived from neuropsychology (e.g. Frisk & Milner 1990; Smith & Milner 1981). It would make the following predictions:

- In a context-dependent episodic memory experiment like the one used in Chapter 8 and 10, using olfactory context-cues, right hippocampal damage would particularly impair context-dependent retrieval cued by odours that are not easily attributed a verbal label (see discussion of Chapter 8) compared to easily nameable odours.
- Right hippocampal damage would impair face recognition in tests like the one used in Chapter 9 - involving faces that are familiar only on a perceptual level (e.g. neighbours, fellow students, faces from advertisement), whereas left hippocampal damage would not cause no such impairment.

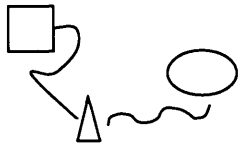
	Left verbal/ narrative	**Right** non-verbal/ conceptual/ geometric
Spatial	"The town is built at the very foot of a range of hills, about 1600 feet high, and rather steep. From its position, it consists of one long, straggling street, which runs parallel to the beach, and wherever a ravine comes down, the houses are piled up on each side of it" (Darwin 1839, p.241).	
Episodic	"She said nothing, but her little eyes kept watching first Peter, as he sprang nimbly hither and thither on his bare feet, clad only in his short light breeches, and then the slim-legged goats that went leaping over rocks and shrubs and up the steep ascents with even greater ease." (Spyri 1986)	

Table 12. 1 Hypothesised function of left and right hippocampus in spatial and episodic memory.

- Right hippocampal damage would cause less impairment on an allocentric spatial memory task, if it could be solved using a narrative mnemonic strategy (e.g. overtly using descriptions of the kind shown in the upper left box of Table 12.1).

Another point of discussion concerns the question of how the characteristics of allocentric topographical memory and of episodic memory can inform each other:

Differences and similarities between topographical memory and episodic memory

View-point-independence of allocentric spatial memory and of context-dependent episodic memory

The following considerations build on a discussion led by Burgess et al. (2002). There, it was argued since spatial memory (navigation) was not just an example of more general episodic memory, that episodic remembering of a route previously taken, recognising landmarks and remembering events that happened there, were not sufficient to generate an accurate trajectory. Further, memories retrieved from both same and different viewpoints could be termed episodic.

However, there does appear to be a link between the viewpoint dependence of patient Jon performing the topographical memory task in Chapter 3 and intact familiarity-based recognition in the context-dependent memory condition of Chapter 8 (see King et al. 2004). Is there also a complementary viewpoint independence in both hippocampal-dependent spatial (e.g. shifted view) and context-dependent episodic memory tasks? As has been argued in the discussion of Chapter 9, it appears indeed that familiar faces are stored and recognised in a viewpoint independent manner, whereas unknown faces are not (Leveroni et al. 2000). This could be further tested in neuropsychological investigations with hippocampal patients using different exemplars of famous faces between study and recognition test. Hippocampal patients would be hypothesised to rely on the perceptual, view-dependent features of the face for successful recognition, whereas normal subjects would be able to use a view-independent representation.

Findings from Chapter 9 and 10 also relate to the question of viewpoint-dependence and episodic memory. The context-dependent episodic memory network, as established in the fMRI studies of Chapter 9 and 10, highly resembles the network supporting retrieval from allocentric spatial memory - as in spatial navigation or memory for spatial scenes - described by Burgess et al. (2002), see also Maguire (2001b). We review the supposed operation of this network below (see highlighted areas). Retrieval is described to arise from an index-like code in the **hippocampus**, which is used to generate an allocentric representation of locations of the elements of a scene in the **parahippocampus** (see also Hartley et al. 2000). This representation is successively translated from allocentric to body-centred to head-centred, supported by the **posterior parietal cortex** (**BA7a,** Andersen 1997; Burgess et al. 1999) and the head-direction system (mammillary bodies, **anterior thalamus** and presubiculum), via the **retrosplenium** (Morris et al. 1999b), into a view-dependent representation for visual imagery, which is hypothesised to be supported by the **precuneus** (see Fletcher et al. 1995). Although this network was proposed for spatial memory, it would be interesting to go in search of viewpoint (in-) dependence for different stages of non-spatial episodic memory retrieval. This could be envisaged using the virtual reality paradigm as implemented in Chapters 8 and 10, by testing context-dependent episodic memory cued by event-location, manipulating the retrieval viewpoint on the cue between study and test and correlating activation in the hypothesised regions of translation (posterior parietal cortex and retrosplenium) with the difference in viewpoint angle. Alternatively, the virtual reality paradigm used in Chapters 3 and 4 could be modified for an fMRI investigation of a correlation between viewpoint-angle increase and engagement of translation areas.

Crossmodal binding

It has been argued that the hippocampus is necessary for crossmodal episodic memory, forming associations between information presented in different modalities or stored in different brain regions (Marr 1971; Mayes et al. 2001; Squire & Zola-Morgan 1991; Teyler & Di Scenna, 1985), and we found evidence of strong hippocampal involvement in multimodal context-dependent memory in Chapter 10. How might this relate to the proposed dissociation between hippocampal-dependent allocentric memory and

hippocampal-independent viewpoint-dependent topographical memory? Bridging this gap is one merit of Eichenbaum's "flexible-relational" memory theory (e.g. Eichenbaum, 2001; Eichenbaum & Cohen, 2001). On the one hand, we could interpret allocentric spatial representations as more flexible than egocentric ones, and on the other hand, we could term the context-dependent episodic memory retrieval as more flexible and relational as compared to familiarity-based recognition. It would be interesting to know of a prediction of this broad theory that could be tested so as to understand further what its implications would be.

For the rest, the crossmodal binding theory of hippocampal function appears to capture but one prominent type of deficit associated with hippocampal damage, whereas further deficits also imply a hippocampal role in the binding of contextual elements from the same sensory modality.

With regard to the binding structure of episodic memory, the results from Chapter 8 contradict the propositions of the Cognitive Map theory in interesting ways. Instead of a map-like spatial – or episodic – memory representation with symmetrical connections between the elements of the map, the finding of independently encoded and retrieved pair-wise associations would allow for "holes and slopes in the map". It seems that such a hypothesis would be hard to investigate using a paradigm like the allocentric topographical memory experiment in humans, but possibly it could inspire computational models and single cell studies in rats. A particularly interesting aspect would seem to be the investigation of retrieval cue hierarchies in spatial memory.

In connection with binding, I would like to add a final reservation to the findings from Chapter 8. Marr's Model (1971) theorised that the hippocampus might rapidly associate neocortical representations of an event via connections with modifiable synapses, ensuring subsequent pattern completion. Transfer of one day's events is hypothesised to occur during the (following) night's sleep. According to this model, the fragmentary pair-wise associations that we measured in Chapter 8 might reflect only a very fragile memory trace that has just begun to form. The memory consolidation would occur much

later and, possibly by means of the recurrent collateral connections, the "holes and slopes" of the map might be smoothed out into a more coherent whole. In order to test for this, we would have to investigate changes in the binding structure in our participants cognitive maps built on the virtual reality context-dependent memory paradigm over at least a day, or associate binding in older memories. Note that Wagenaar (1986), investigating memories over four years, still found retrieval asymmetries, which might suggest that our results might in fact generalise to older memories.

Is there an episodic-semantic-like distinction in spatial memory?

As Burgess et al. (2002) note the gradual learning of environmental spatial knowledge seems to correspond more to ideas of semantic than episodic memory. Interestingly, this statement seems to imply a temporal distinction between instantly formed episodic-like spatial representations and long-term built semantic spatial representations. This may relate to an fMRI study by Niki & Luo (2002): It was found that memories for places subjects had visited within the last 2 years were associated with medial temporal activation (including the hippocampus) when compared to memories for places visited more than 7 years before. Further analyses revealed that this medial temporal lobe activity was not due to the fact that the retrieval of recent memories was accompanied by more details. In fact, we would hypothesise that this type of memory was semantic in quality and thus differed from contextual-rich hippocampal-dependent autobiographical memory. In addition, several authors have provided evidence of retained spatial memories from childhood and early adolescence in amnesic patients, inclusive of information about salient landmarks, routes and directions, adequate for navigation (Teng & Squire, 1999; in Ryan et al. 2001), which could all be categorised as "spatial semantic", being less vivid and contextual-rich than remote topographical memories in normal subjects (Moscovitch et al.,1999, in Ryan et al. 2001; see also Rosenbaum et al. 2000). These data imply that hippocampal dependence may result from recent context-rich encoding rather than allocentric spatial encoding. However, it may still be that the recent hippocampal-dependent spatial representations are more allocentric or "flexible" (Eichenbaum & Cohen 2001) in being naturally amenable to retrieval from novel

viewpoints, while older spatial memories are better supported by less flexible, over-learned, procedural, or route-like representations in the absence of hippocampal support (e.g. Hartley et al. 2003; Poltrack et al. 2001).

Nonetheless, the apparent difficulty of existing theories of hippocampal function to reconcile the episodic-semantic and allocentric-egocentric distinctions indicate that the further investigation of spatial semantic memory would be a promising way to explore the inter-relation between semantic and episodic memory (over time), and the role of the hippocampus. Over all it seems that the facts speak against an undifferentiated role of the hippocampus in memory for facts and contextual-rich event memory, as proposed by the declarative memory theory (Manns & Squire, 1999; Squire & Zola-Morgan, 1991; Zola et al., 2000), as well as being problematic for an interpretation of the hippocampus as a non-time-limited cognitive map (O'Keefe & Nadel 1978)

Episodic memory in normal ageing and Alzheimer's disease

Finally, on the basis of the comparability of allocentric topographical memory and context-dependent episodic memory in terms of hippocampal affordance, as further corroborated by patient Jon's impairments on both (see King et al. 2004), we would expect to find a significant impairment on the context-dependent episodic memory experiment of Chapter 8 and 10 in patients with probable early Alzheimer's disease. Moreover, we would also expect to find a significant effect of ageing for the context-dependent condition but not the familiarity-based object recognition condition in normal healthy subjects.

Conclusion

In summary, I have investigated the role of the human hippocampus in spatial and episodic memory with a specific focus on allocentric representations in spatial memory and context-dependent memory for events. I have developed a difficulty-matched test of allocentric topographical memory compared to egocentric memory and shown that hippocampal damage leads to selective deficits. This has further been used to show that a selective deficit in allocentric spatial memory can be a cause of topographical disorientation, and is under continued development for use in early detection of

Alzheimer's disease. Another virtual reality paradigm for probing the content of event memory via several different context-cues was used to investigate the nature of the binding together of different aspects of an event, which turned out to be neither holistic nor symmetrical. In addition I have used fMRI to probe the neural bases of episodic memory, with particular emphasis on retrieval of cross-modal (spatial and olfactory) contextual information and the roles of vividness, semantic embedding and personal relevance in hippocampal processing.

In conclusion, our findings suggest the hippocampus binds together neocortical representations (Marr 1971) for long-term retention to provide view-point independent, contextual-rich retrieval of memories such as allocentric spatial representations and multi-sensory event-representations.

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